Sequential Multicomponent Strategy for the Diastereoselective Synthesis of Densely Functionalised Spirooxindole-fused Thiazolidines

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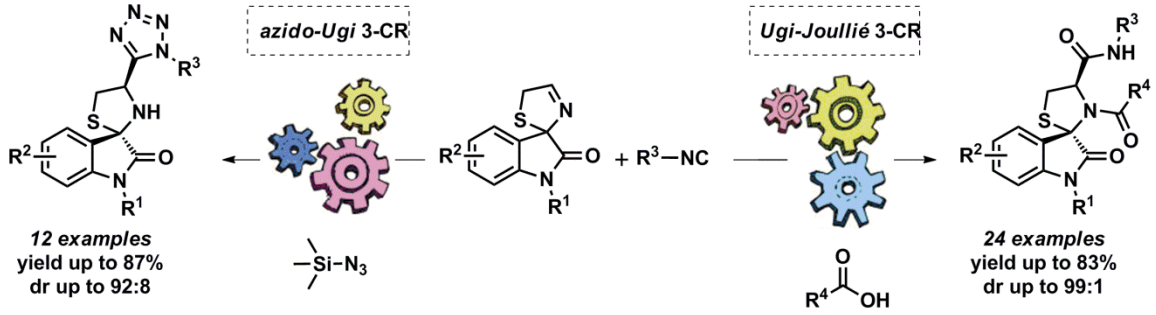


Abstract

We developed two Ugi-type three-component reactions of spirooxindole-fused 3-thiazolines, isocyanides and either carboxylic acids or trimethylsilylazide, to give highly functionalized spirooxindole-fused thiazolidines. Two diverse libraries were generated using practical and robust procedures affording the products in typically good yields. The obtained thiazolidines proved to be suitable substrates for further transformations. Notably, both the Ugi-Joullié and the azido-Ugi reactions resulted highly diastereoselective, affording predominantly the *trans*-configured products, as confirmed by X-ray crystallographic analysis.

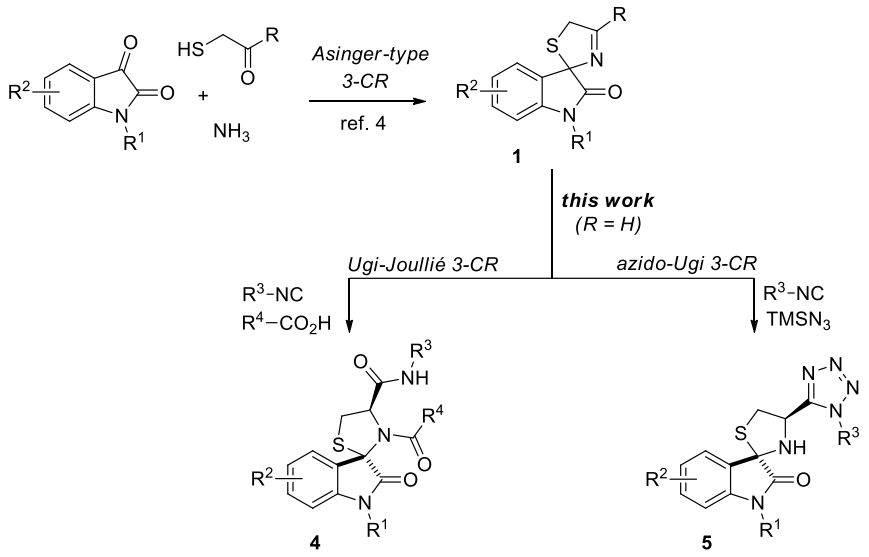
Keywords:

Thiazolidine, spirooxindole, multicomponent reactions, Asinger reaction, Ugi-Joullié reaction, azido-Ugi reaction.

Introduction

The field of diversity-oriented synthesis (DOS)[1] has matured considerably since its introduction in the early 2000s, providing numerous approaches for the generation of molecular diversity. The main challenge for DOS is the proper combination of a central scaffold diversity with a high degree of peripheral structural variability, considering scaffold diversity the most important feature for the specific interaction with the biological environment. In this regard, spirocycles have become attractive synthetic targets in drug discovery projects, for their inherent three-dimensional nature and concomitant ability to project functionalities in all three dimensions. Variation brought by appendage diversity, usually resulting in the variation of R-groups around a single scaffold, is less challenging but equally significant, taking into account that wider is the degree of structural variation among compounds within a library, the higher is the chance of achieving broad or distinct biological activity across that library.

The goal of molecular diversity requires the application of efficient synthetic strategies, possibly involving a divergent approach, which allows the transformation of a small number of starting materials into many distinct structures. Owing to their ability to rapidly construct highly functionalized molecular scaffolds from simple precursors, multicomponent reactions (MCRs) can be considered excellent tools for DOS applications.[2] As part of our ongoing interest in 3,3-disubstituted oxindoles and spiro-fused analogues,[3] we have recently reported the synthesis of spirooxindole-fused 3-thiazolines by means of an Asinger-type three-component reaction (structure **1**, Scheme 1).[4]



Scheme 1. The two sequential multicomponent strategies described in this work.

Spirooxindole-fused 3-thiazolines **1** represent an underexploited scaffold in the context of sulfur-containing spirooxindoles. They are in themselves endowed with R, R^1 and R^2 diversity, but can be also regarded as versatile intermediates towards peripheral diversity, because of the presence of the reactive C=N double bond.

We demonstrate here the suitability of such spiro compounds as useful substrates for two highly diastereoselective, multicomponent transformations, namely the Ugi–Joullié and the azido-Ugi reaction, to give libraries of compounds **4** and **5**, respectively. Although the strategy of sequential Asinger and Ugi reactions is already reported, mainly by Martens and coworkers,[5] its extensive application to spirocyclic imines is quite unprecedented, as well as the issue of diastereoselectivity has never been addressed so far.

The unique application of the Asinger 4-CR/azido-Ugi 3-CR combination was reported by Dömling and coworkers,[6] while, quite recently, the first example of diastereoselective azido-Ugi reaction was reported by Nenajdenko and coworkers,[7] employing secondary amines. Summing, at the best of our knowledge, no examples of diastereoselective multicomponent transformations have been reported until now on thiazoline substrates.

Being aware of the potential biological implication of this work and considering typical substituent patterns of bioactive related compounds (Figure 1),[8] we provided to decorate the central spiro scaffold with a variety of lipophilic and polar functional groups, as well as with the pharmacological relevant tetrazole ring.

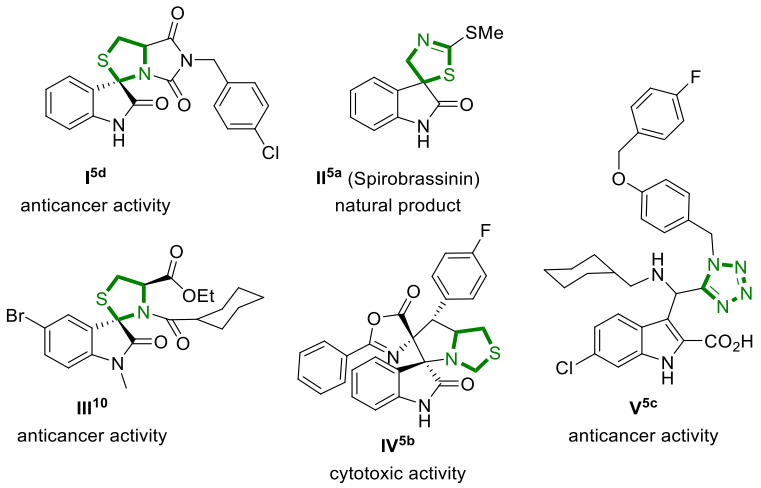


Figure 1. Examples of biologically relevant compounds containing spirooxindoles, thiazolidine and tetrazole moieties.[8]

By means of simple and rapid protocols, thirty-six compounds have been overall prepared, showing a wide degree of appendage diversity and a high diastereoisomeric ratio in most cases (dr up to 99:1 for the Ugi-Joullié and 98:2 for the azido-Ugi).

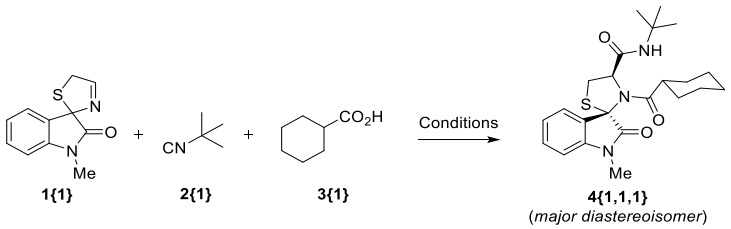
Results and Discussion

Initially, racemic isatin-derived thiazoline **1{1}**, *tert*-butyl isocyanide **2{1}** and cyclohexyl carboxylic acid **3{1}** were selected to optimize the conditions for the Ugi-Joullié reaction (Table 1).

Relying on reaction conditions already reported for cyclic imines,[9] we started considering aprotic solvents such as dichloromethane and toluene (entries 1-2), but the reaction was found to be sluggish. Working in more usual solvents for Ugi-type processes[10] (MeOH, entry 3), the same reaction afforded the desired thiazolidine product in 55% yield as a readily separable 1:1 mixture of *trans* and *cis* diastereoisomers. Switching to more acidic trifluoroethanol (TFE) increased the reaction rate and yield (entry 4). It also favored a more diastereoselective process,[11] leading to *trans*-isomer **4{1,1,1}** as the major product (dr 75:25). The dr was further improved by increasing the concentration (0.5 M, entry 5), while either lowering the

concentration (entry 6) or running the reaction at 0 °C (entry 7) reduced the conversion without improving the dr.

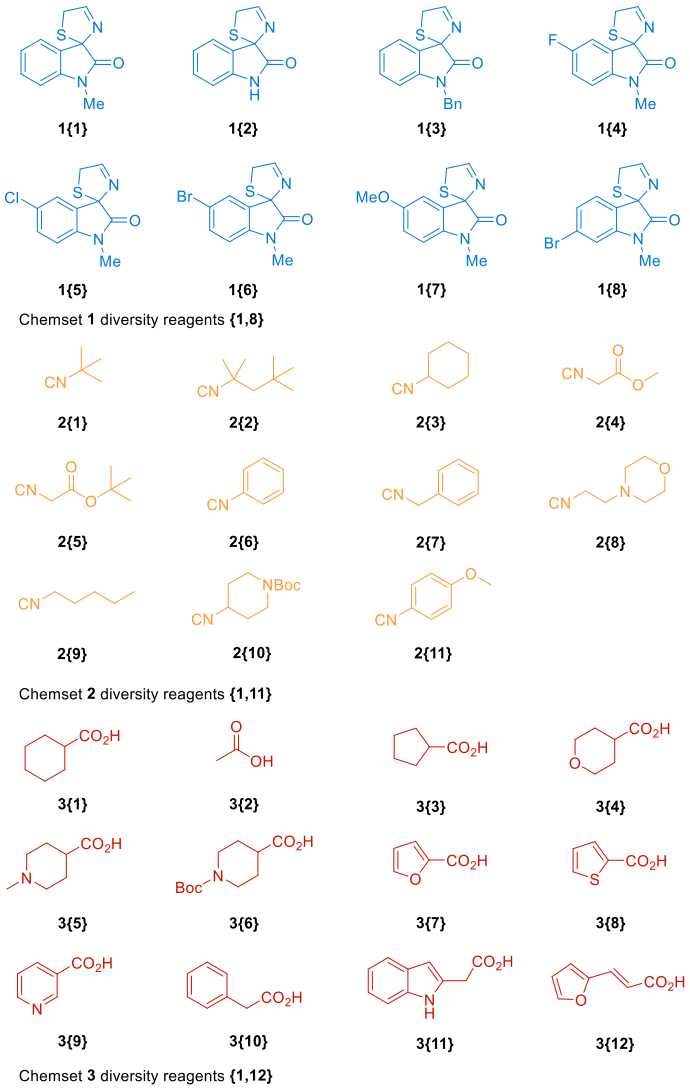
Table 1. Optimization of the Ugi-Joullié 3-CR.[a]



Entry	Solvent	Conc. [M]	Time [h]	Conversion (%)[b]	dr [*trans*:*cis*][c]
1	CH_2Cl_2	0.25	24	trace	nd
2	Toluene	0.25	24	trace	nd
3	MeOH	0.25	24	55	50:50
4	TFE	0.25	6	95	75:25
5	**TFE**	**0.5**	**4**	**95 (83)[d]**	**87:13**
6	TFE	0.125	6	85	76:24
7[e]	TFE	0.25	6	85	74:26

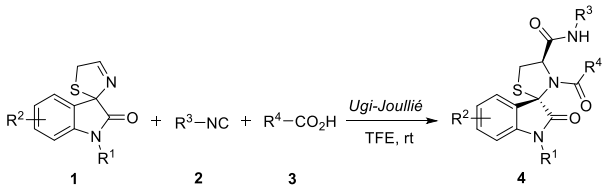
[a] Reactions were performed on a 0.3 mmol scale, with **1{1}:2{1}:3{1}** in a 1:1:1 ratio, at room temperature, unless otherwise indicated. [b] Evaluated by ^{1}H NMR analysis of the crude mixture considering both diasteroisomers. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Isolated yield for the *trans* diasteroisomer. [e] Reaction performed at 0 °C. TFE = 2,2,2-trifluoroethanol. nd = not determined.

Figure 2. Chemsets: thiazolines Chemset **1**, isocyanides Chemset **2** and carboxylic acids Chemset **3**.

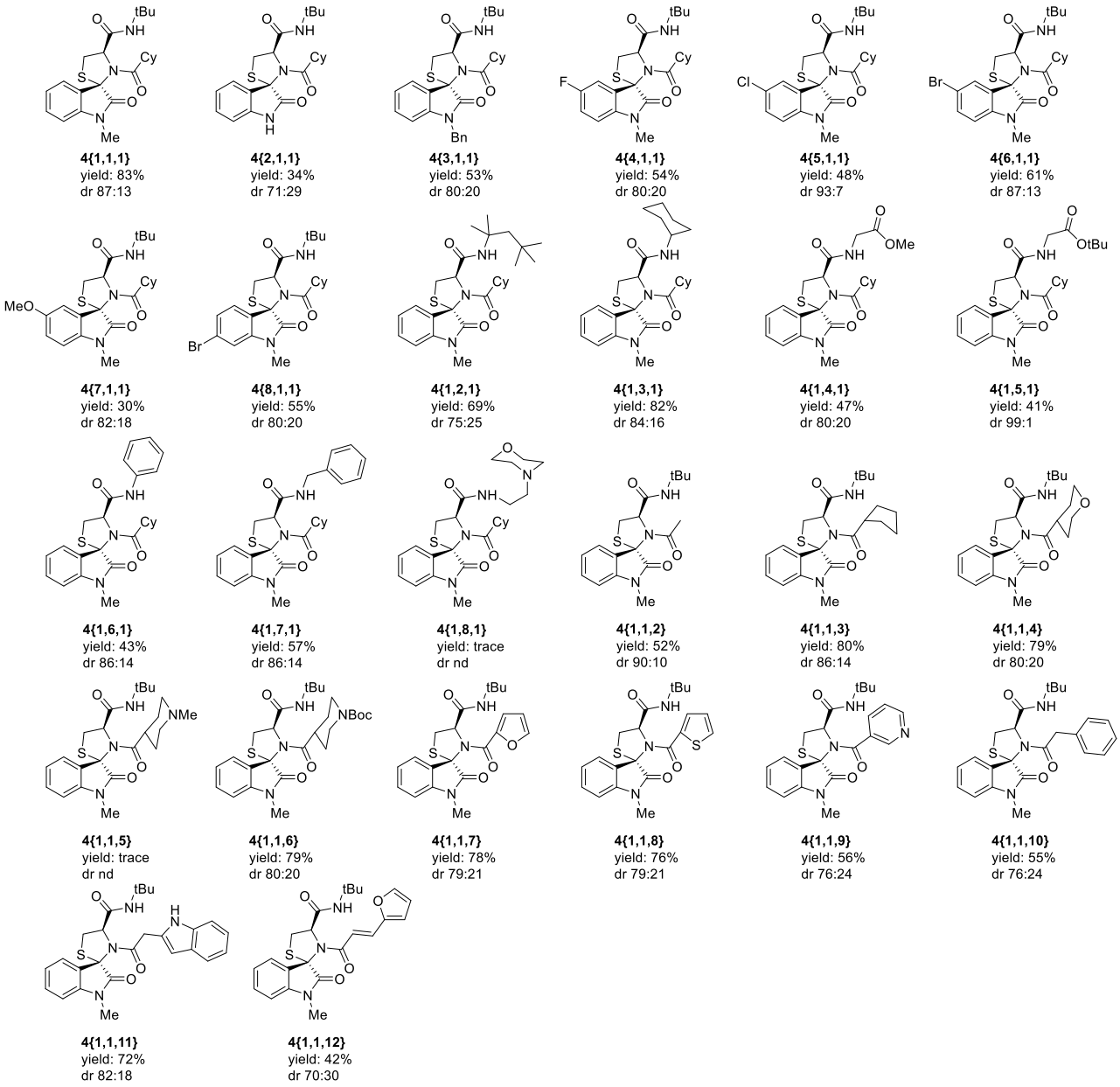


With the optimal conditions in hand, we investigated the scope and limitations of the protocol, varying the three components one at a time (Scheme 2, for reagents input see Figure 2). Reaction of oxindole-based thiazolines **1{1-8}** with *tert*-butyl isocyanide **2{1}** and cyclohexanecarboxylic acid **3{1}** afforded the expected products **4{1-8,1,1}** with good dr (up to 93:7 for compound **4{5,1,1}**) and in generally reasonable to good yield, although moderate yields were observed for **4{2,1,1}** and **4{7,1,1}**. Next, different isocyanides **2{1-8}** were combined with thiazoline **1{1}** and carboxylic acid **3{1}**. Compounds **4{1,1-8,1}** were obtained in acceptable yields, with aliphatic isocyanides affording the best results (69% and 82% yield for compounds **4{1,2,1}** and **4{1,3,1}**, respectively). Due to their lower stability in acidic media, isocyanoacetates **2{4,5}** gave products **4{1,4,1}** and **4{1,5,1}** in lower yields.

Scheme 2. Scope of the Ugi-Joullié 3-CR.[a]



1 2 3 4



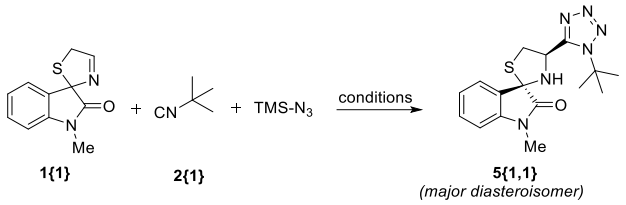
[a] Reactions were performed on a 0.3 mmol scale with **1:2:3** in a 1:1:1 ratio. Yields refer to isolated yield of the *trans* diasteroisomer. The dr's were determined by ^{1}H NMR analysis of the crude product (see the Supporting Information (SI) file, where such analysis is reported for compound **4{1,6,1}**, as an example). nd = not determined.

However, the highest dr was achieved in the reaction with *tert*-butyl isocyanoacetate (**4{1,5,1}**, dr 99:1). Good results were obtained with both phenyl and benzyl isocyanide (**4{1,6,1}** and **4{1,7,1}**), whereas no product **4{1,8,1}** was observed in the reaction with 2-morpholinoethyl isocyanide **2{8}**.[12] Finally, twelve different carboxylic acids were tested in the reaction with thiazoline **1{1}** and *tert*-butyl isocyanide **2{1}**. The resulting products **4{1,1,1-12}** were obtained in generally high yields (up to 80%) and with satisfactory dr (up to 86:14), except compound **4{1,1,5}** that was detected only in trace amounts. In this case, most likely the employed carboxylic acid [*N*-methylpiperidine-4-carboxylic acid] **3{5}** was present in its zwitterionic form and therefore not reactive. In support of this hypothesis, the reaction with the 1-(*tert*-butoxycarbonyl)-piperidine-4-carboxylic acid **3{6}**, structurally similar but lacking basicity, furnished the expected UJ-3CR product **4{1,1,6}** in good yield and dr. The wide variety of successfully tested carboxylic acids is noteworthy, ranging from phenylacetic acid to carboxylic acids containing both electron-rich and electron-deficient heterocycles (**3{7-12}**).

We then moved on to the azido-Ugi process, optimizing the reaction conditions using racemic thiazoline **1{1}**, *tert*-butyl isocyanide **2{1}** and trimethylsilyl azide as the inputs (Table 2). Also in this case, the reaction was found to be sluggish in dichloromethane and toluene (entries 1-2), whereas excellent conversions to the target tetrazole derivative **5{1,1}** were observed in polar protic solvents (entries 3-5). As for the above UJ-3CR, fluorinated solvents (TFE and 1,1,1,3,3,3-hexafluoro-2-propanol, HFIP) led to a more a diastereoselective transformation, affording the *trans* diastereoisomer **5{1,1}** as the major compound.

Aiming to further improve the dr, different concentrations and temperatures were screened. We found that increasing the concentration in TFE led to a slight decrease in dr (entry 6), whereas lowering the temperature only gave a small improvement in dr (entry 7). Similarly, varying the concentration in HFIP did not lead to an appreciable improvement (entries 9,10), while in this case excellent diastereoselectivity was achieved at 0 °C (entry 11).

Table 2. Optimization of the azido-Ugi 3-CR.[a]



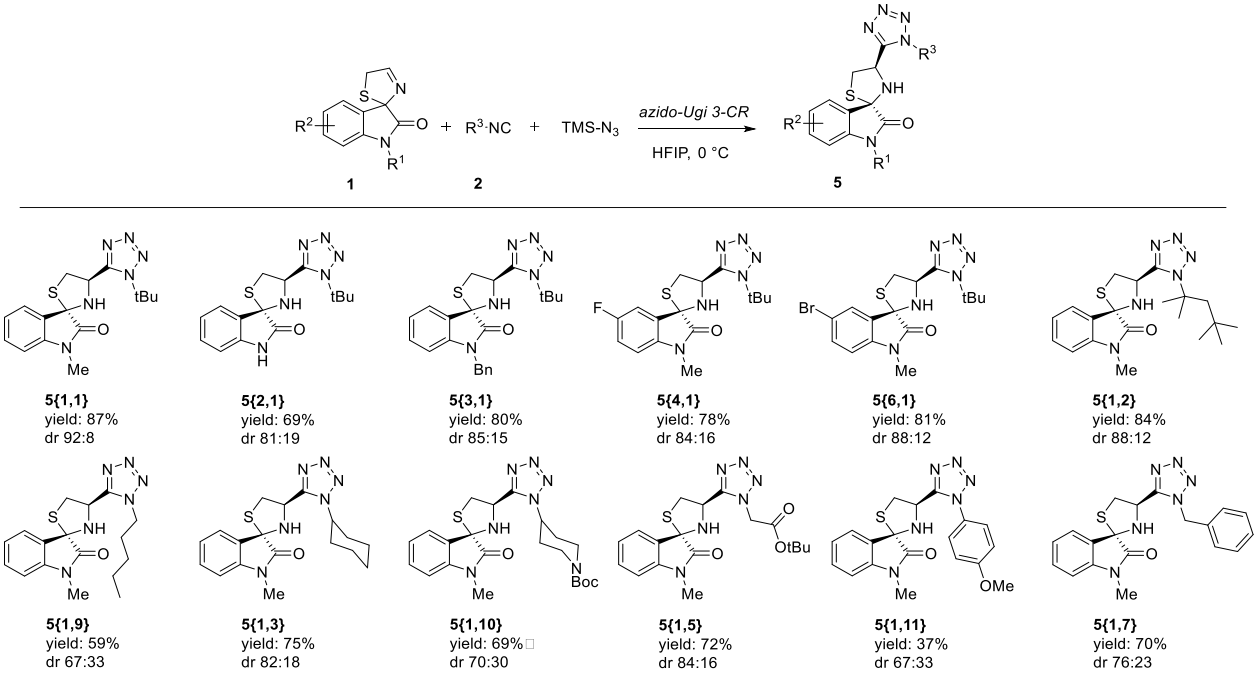
Entry	Solvent	Conc. [M]	Time [h]	Conversion (%)[b]	dr [*trans:cis*][c]
1	CH_2Cl_2	0.5	24	<5	nd
2	Toluene	0.5	24	<5	nd
3	MeOH	0.5	2	95	56:44
4	TFE	0.5	1	99	81:19
5	HFIP	0.5	1	99	85:15
6	TFE	1.0	1	99	78:22
7	TFE[d]	0.5	1	99	83:17
8	TFE[e]	0.5	1	99	83:17
9	HFIP	1.0	1	99	84:16
10	HFIP	0.05	1	99	82:18
11	HFIP[d]	0.5	1	99 (87)[f]	92:8

[a] The reactions were performed on a 0.15 scale with **1{1}:2{1}:**TMS-N_3 in a 1:1:1 ratio, at room temperature unless otherwise noted. [b] Evaluated on the crude mixture considering both diasteroisomers. [c] Determined by ^{1}H NMR on the crude mixture. [d] Reaction performed at 0 °C. [e] Reaction performed at -18 °C. [f] Isolated yield for the *trans* diasteroisomer. TFE = 2,2,2-trifluoroethanol. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. nd = not determined.

Next, we investigated the reaction scope, combining thiazolines **1{1-4}** and **1{6}** and isocyanides **2{1-3}, 2{5}, 2{7}, 2{9-11}** with trimethylsilyl azide, leading to good results in nearly all cases (Scheme 3). When aliphatic isocyanides were used, the corresponding products (**5{1-4,1}** and **5{6,1}, 5{1,2}, 5{1,9}, 5{1,3}, 5{1,10}, 5{1,5}**) were obtained in satisfactory yield and dr, with the exception of **5{1,9}** (67:33 dr). Unlike the case of the UJ-3CR, *tert*-butyl isocyanoacetate **2{5}** also worked well in the azido-Ugi reaction, affording the desired

product **5{1,5}** in 72% yield and with 84:16 dr. Finally, phenyl isocyanide **2{11}** behaved similarly as in the UJ-3CR, giving the corresponding product **5{1,11}** in moderate yield and dr.

Scheme 3. Scope of components in the azido-Ugi 3-CR.[a]



[a] Reactions were performed on a 0.3 mmol scale, with **1{1}:2{1}:**TMS-N_3 in 1:1:1 ratio. For each product, the isolated yield for the *trans* diasteroisomer is reported. The indicated dr was determined by ^{1}H NMR on the crude mixture. Compound **5{1,10}** was obtained as a mixture of inseparable diastereoisomers.

To determine the relative configuration for the two product types (**4** and **5**), single crystals of **4{1,1,1}** and **5{1,1}** were subjected to X-ray crystallographic analysis, leading to the unambiguous assignment of the *trans* stereochemistry for both compounds (Figure 3).

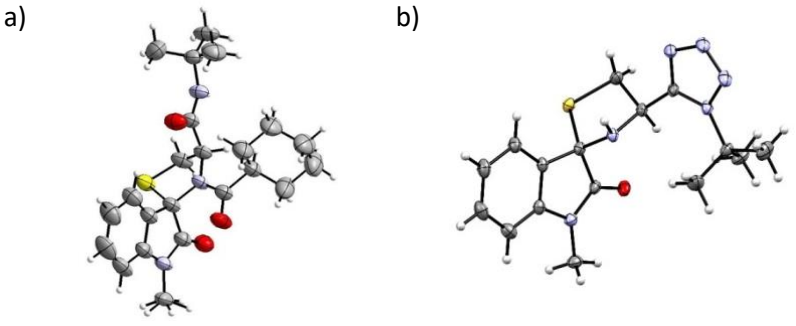
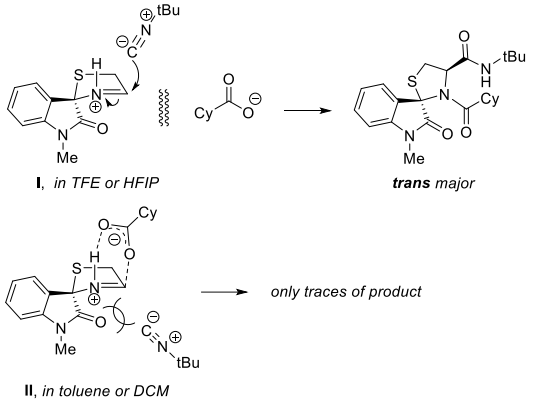


Figure 3. a) ORTEP view of compound **4{1,1,1}** at room temperature. The methyl group on the left is rotationally disordered (see SI). Thermal ellipsoids of non-H atoms were drawn at the 50% probability level. b) ORTEP view of compound **5{1,1}** at T = 105 K. Thermal ellipsoids of non-H atoms were drawn at the 50% probability level.

Since all products **4** and **5** were obtained under the same conditions employed for compounds **4{1,1,1}** and **5{1,1},** respectively, and given common trends in ^{1}H NMR chemical shifts as well as similarities in TLC retention factors (the *trans*-diastereoisomer always shows major R_f with respect to the *cis*- one), the same relative *trans*-stereochemistry was assigned to all products **4** and **5**.

To provide a plausible explanation for the highly diastereoselective outcome of both reactions, we consider the mechanism proposed in Figure 4 for the UJ-3CR. We presume that the preferred conformation of imine **1{1}** in solution is mainly determined by the spiro junction between the oxindole and the thiazoline ring system, with the latter adopting an envelope-like conformation oriented nearly perpendicularly with respect to the oxindole. This spatial arrangement highlights the substantial shielding of the *Si*-face of the imine for both steric and electronic reasons, mainly due to the proximity of the oxindole carbonyl. As a consequence, in strongly hydrogen-bonding solvents such as TFE and HFIP, the protonated imine exposes the convex *Re*-face to the incoming isocyanide, affording predominantly the *trans* isomer (Figure 4, **I**). Taking into account the effect of the solvent on the diastereoselectivity of the UJ-3CR involving a five-membered cyclic imine, as reported by Katsuyama *et al.*,[11a] we can also rationalize the poor reactivity observed in toluene. Indeed, in such nonpolar solvents, the protonation of the imine by the carboxylic acid likely results in the formation of a contact ion pair. This close interaction lowers the overall electrophilic reactivity of the imine and, more decisively, hinders the approach of isocyanide, shielding the sterically more available *Re*-face (Figure 4, **II**).

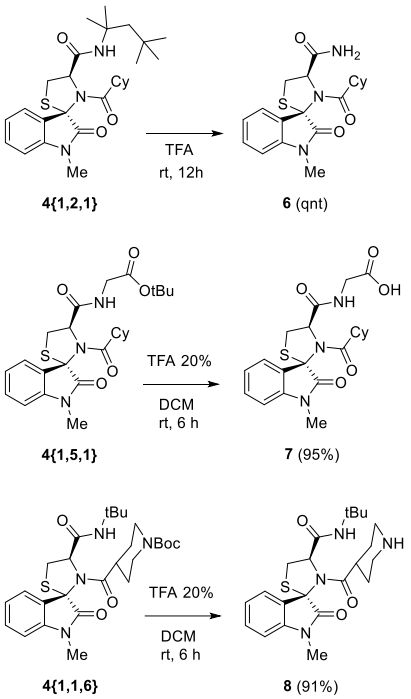
Figure 4. Plausible explanation of the stereochemical outcome for the UJ-3CR.



The use of MeOH as the solvent represents an intermediate scenario, providing sufficient activation for the reaction to occur, but very limited discrimination between the diastereotopic faces. Similar considerations on the molecular conformation of the imine component can be made to rationalize the high dr observed in the azido-Ugi 3-CR, that represented the first highly diasteroselective example on thiazoline-based compounds.

Having established the reaction scope, further transformations were examined to extend the library of potentially useful compounds. Selected post-transformations of Ugi-Joullié products **4** are depicted in Scheme 4. Primary amide **6** is readily obtained by treatment of compound **4{1,2,1}** with trifluoroacetic acid. Starting from compound **4{1,5,1}**, cleavage of the *tert*-butyl ester afforded the free acid **7** in quantitative yield. Finally, the piperidine derivative **8** was obtained treating compound **4{1,1,6}** with 20% TFA in dichloromethane. The presence of unprotected primary amide, carboxylic acid and secondary amine groups in compounds **6**, **7** and **8** respectively, can be of interest for modulation of drug-like properties. Moreover, it makes such transformed compounds also suitable for further elaborations, included application in peptidomimetic chemistry.

Scheme 4. Further post-transformation reactions on selected UJ-3 CR products.



In order to evaluate if our compounds were suitable in drug discovery programs, we calculated their physicochemical properties using DruLiTo[13] (all calculation details are provided in the SI file). Almost all compounds were drug-like according to the Rule of Five (Ro5) proposed by Lipinski,[14] with only a few of them exceeding the limit of 500 MW. All compounds have calculated octanol/water partition (LogP) lower than 5, with the highly hydrophilic area (LogP < 3) mostly populated (**Figure 5**).

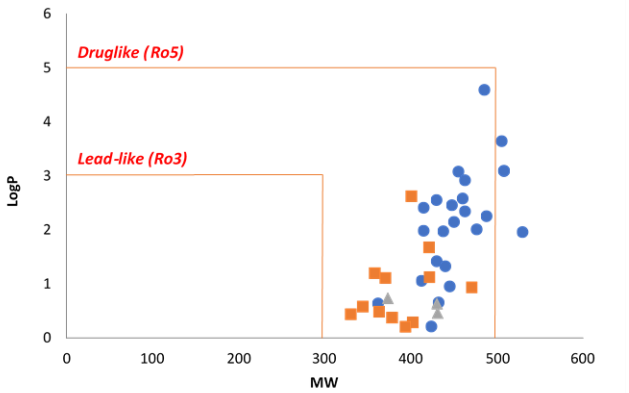


Figure 5. Drug- and lead-likeness (MW/LogP) of all the products obtained in this work. Blue-spots: Ugi-Joullié products **4**, orange-spots: azido-Ugi products **5**, grey-spots: post-transformation products **6**,**7** and **8**.

Concerning the other Ro5 properties, all the synthesised compounds have hydrogen bonding donator groups (HBD) lower than five and hydrogen bonding acceptor groups (HBA) lower than 10 (**Figure 6**). These data, and in addition the presence of rotational bonds (RB) lower than 10 and the polar surface area prediction (TPSA) lower than 140 $Å^2$ (see SI), according to Veber's rule,[15] make definitively our compounds of potential interest from the pharmacological point of view.

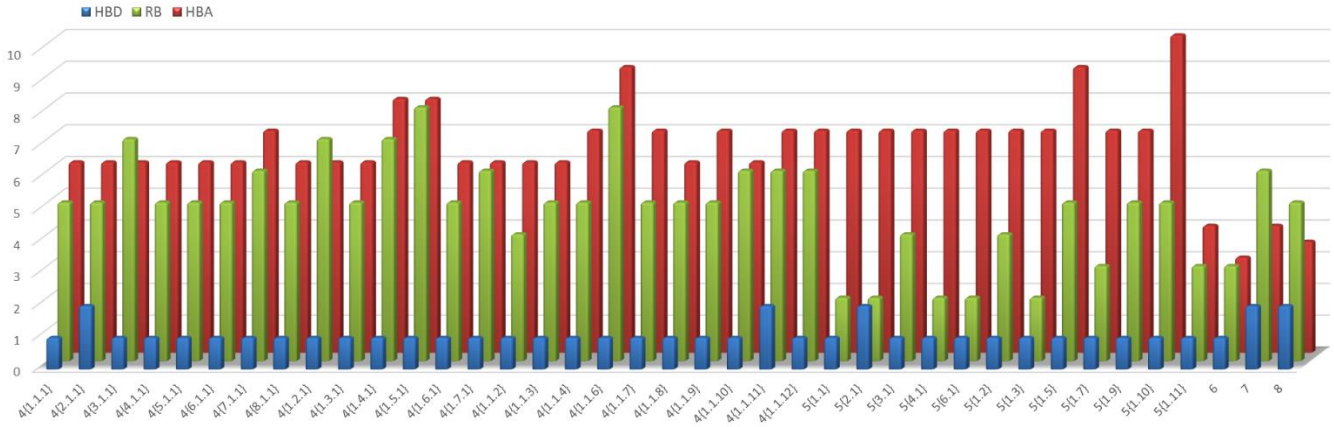


Figure 6. Calculated hydrogen bonding donators (HBD, blue-bars), hydrogen bonding acceptors (HBA, red-bars) and rotational bonds (RB, green-bars) for all the synthesised compounds.

Conclusions

In conclusion, we have efficiently synthesized two structurally diverse libraries of highly functionalized spiooxindole thiazolidines, *via* Ugi-Joullié and azido-Ugi multicomponent reactions. The MCR-derived central spiro scaffold was effectively functionalized with a variety of lipophilic and polar appendages, as well as with tetrazole as a carboxylic acid isostere. The products were obtained in generally high yields, with simple workup procedures and straightforward isolation. The observed high diastereoselectivity for both the transformations is particularly noteworthy. Given the interesting physicochemical properties of these products, biological evaluation[16] of compounds **4** and **5** is currently ongoing in collaboration with Merck Pharma®.

Experimental Section

General remarks and chemicals All commercial materials (Aldrich, Fluka, Fluorochem) were used without further purification. All solvents were of reagent grade or HPLC grade. Reactions requiring anhydrous conditions were performed under nitrogen atmosphere. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light (254 nm) or by treatment with $KMnO_4$ solution in water or ninhydrin solution in ethanol. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). ^{1}H NMR spectra and ^{13}C NMR, COSY, HSQC and HMBC spectra were recorded on 300, 400 and 500 MHz spectrometers. ^{13}C NMR spectra have been recorded using the APT pulse sequence. The number of carbons reported in the ^{13}C data are derived from the HMBC (Heteronuclear Multiple Bond Correlation) experiment. Chemical shifts are reported in parts per million relative to the residual solvent. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra (HR-MS) were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Thiazolines **1** were synthesized according to our previous work.[4]

Representative procedure for Ugi-Joullié 3-CR reaction. To a solution of thiazoline **1{1}** (0.3 mmol, 1 eq) in TFE (0.62 mL), isocyanide **2{1}** (0.3 mmol, 1 eq) and the carboxylic acid **3{1}** (0.3 mmol, 1.0 eq) were added at room temperature. The reaction was stirred and the conversion was monitored by TLC. The solvent was removed under reduced pressure and the crude was purified by flash chromatography (FC) obtaining the pure *trans*-diastereoisomer (R_f major, with respect to the *cis*-diastereoisomer), which was fully characterised as reported below.

(3S*,4'R*)-*N*-(*tert*-butyl)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (4{1,1,1}). FC: CH_2Cl_2:EtOAc, 95:5; yield: 83%; grey foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 4:1 mixture of two rotamers) δ 7.43-7.18 (m, 2H), 7.11 (t, br, *J* = 7.8Hz, 0.2H), 7.14 (t, br, *J* = 7.8Hz, 0.8H), 6.95-6.86 (m, br, 0.4H), 6.83 (d, br, *J* = 7.8Hz, 0.8H), 6.52 (m, br, 0.8H), 5.42 (d, br, *J* = 4.9 Hz, 0.2H), 4.89 (d, *J* = 7.8 Hz, 0.8H), 4.04 (dd, *J* = 11.6 and 6.9 Hz, 0.8H), 3.69-3.57 (m, 0.4H), 3.45 (d, *J* =

11.6 Hz, 0.8H), 3.26 (s, 0.6H), 3.22 (s, 2.4H), 2.25 (t, br, J = 10.7Hz, 0.8H), 1.84-1.08 (m, 10H methylene protons + 0.2H), 1.47 (s, 7.2H), 1.40 (s, 1.8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 175.6 and 175.0 (1C), 169.2 and 168.8 (1C), 143.7 and 142.2 (1C), 130.8 and 130.1 (1C), 127.3 and 126.1 (1C), 124.3 and 123.8 (1C) 122.8 and 122.3 (1C), 109.1 and 108.9 (1C), 71.8, 66.8 and 66.2 (1C), 52.1 and 52.3 (1C), 44.1 and 42.7 (1C), 33.4, 29.9 and 29.6 (2C), 28.7 (3C), 26.6, 25.4 and 25.3 (3C); HR-MS (ESI) calcd for $C_{23}H_{31}N_3NaO_3S^+$ ($[M+Na]^+$) 452.1978, found 452.1987.

Representative procedure for azido-Ugi 3-CR reaction. To a solution of thiazoline **1{1}** (0.3 mmol, 1 eq) in HFIP (0.68 mL) cooled to 0 °C, isocyanide **2{1}** (0.3 mmol, 1 eq) and trimethylsilyl azide (0.3 mmol, 1 eq) were added. The reaction was stirred at the same temperature and the conversion was monitored by TLC. The solvent was evaporated under reduce pressure and the crude was purified by flash chromatography (FC) obtaining the pure *trans*-diasteroisomer (R_f major, with respect to the *cis*-diastereoisomer), which was fully characterised as reported below.

(3S*,4'R*)-4'-(1-(*tert*-butyl)-1H-tetrazol-5-yl)-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (5{1,1}). FC: CH_2Cl_2:EtOAc, from 100:0, to 96:4; yield: 87%; amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.38 (td, J = 7.6, 1.3 Hz, 1H), 7.15 (td, *J* = 7.6, 1.3 Hz, 1H), 6.88 (d, *J* = 7.6, 1H), 5.80 (dd, *J* = 9.5, 6.3 Hz, 1H), 4.00 - 3.90 (m, 1H), 3.75 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.22 (s, 3H), 2.85 (br s, 1H), 1.81 (s, 9H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 176.4, 152.6, 143.3, 130.7, 126.4, 124.1, 123.6, 108.7, 75.5, 62.1, 57.3, 41.0, 30.0 (3C), 29.8; HR-MS (ESI) calcd for $C_{16}H_{21}N_6OS^+$ $[MH]^+$ 345.1492, found 345.1512.

Associated Content

The Supporting Information is available free of charge on the ACS publications website at DOI:xxxxxxxxxx.

- Crystallographic information file for **4{1,1,1}** (CIF)
- Crystallographic information file for **5{1,1}** (CIF)
- General remarks and chemicals, general procedures for Ugi-Joullié 3-CR and azido-Ugi 3-CR, spectroscopic and spectrometric data for compound **4**,**5** and **6-8**, example of evaluation of the diasteroisomeric excess by ^{1}H NMR (compound **4{1,6,1}**), spectral copies of ^{1}H and ^{13}C NMR of

compounds **4**,**5** and **6-8**, crystal structures of **4{1,1,1}** and **5{1,1}**, table of calculated physicochemical properties for all the synthesized compounds. (PDF)

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Author Contributions

Rainoldi G., Silvani A. and Ruijter E. conceived and designed the experiments; Begnini F. and De Munnik M. performed the experiments; Lo Presti L. and Vande Velde C. M. L. performed the X-ray analysis; Lesma G., Orru R. and Ruijter E. analyzed the data and contributed reagents/materials/analysis tools; Rainoldi G. and Silvani A. wrote the paper. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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(16) Given the high structural similarity of compounds **4** to **III** reported in Figure 1 displaying potent anticancer activity, a selection of these compounds were submitted to the NCI-60 human tumor cell lines screen. Unfortunately, none of the submitted compounds showed significant anticancer activity at 10 μM concentration.