RESEARCH ARTICLE doi.org/10.1002/adsc.202500166 ADVANCED SYNTHESIS & CATALYSIS

Asymmetric Synthesis of Highly Substituted Spiro[*2H*-pyrrole-2,3-Succinimide] Derivatives by Copper-Catalyzed Post-Ugi Reactions

Javier Gómez-Ayuso,[a] Israel Carreira-Barral,[a] Roberto Quesada,[a] and María García-Valverde[a,*]

[a] Departamento de Química,
Facultad de Ciencias,
Universidad de Burgos, 09001, Burgos, Spain
E-mail: magaval@ubu.es

Manuscript received: February 11, 2025; Revised manuscript received: March 21, 2025;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202500166

Abstract: Herein we present a novel one-pot methodology for the synthesis of enantioenriched 2*H*-pyrrolespirosuccinimides by copper-catalyzed reactions on Ugi adducts derived from enantiopure α-alkylbenzyl amines through a chirality transfer process. We have proposed a mechanism, supported by density functional theory (DFT) calculations, where a hydrogen radical-shuttle (HRS) process explains the chemical and stereochemical results. This work demonstrates the efficient stereoselective synthesis of structurally unique, highly functionalized nitrogen heterocyclic systems using simple protocols and affordable starting materials.

Keywords: multicomponent reactions; radical reactions; copper catalyst; succinimide; spirosuccinimide; spiro-2*H*-pyrrole

1. Introduction

The development of novel methodologies for the synthesis of nitrogen heterocyclic compounds is key to the pharmaceutical industry, as a significant proportion of marketed drugs feature active ingredients containing at least one nitrogen heterocycle core.[1] This is exemplified by prominent scaffolds like five-membered nitrogen heterocycles such as succinimides[2] or pyrroles.[3] Spirocyclic compounds represent an intriguing class of organic molecules defined by their unique three-dimensional architecture, where two cyclic systems are connected through a single tetrahedral spiro center, being their spatial arrangement and hence their stereochemistry critical.[4] This structural motif imparts exceptional conformational rigidity and stereochemical precision, making them ideal for pharmacophore modelling, thus highly advantageous in medicinal chemistry and drug discovery.[5]

Their structural features enhance drug-target recognition, improve physicochemical properties, and contribute to their biological activities such as anticancer, antidepressant and antimicrobial effects. The access to spiro scaffolds, especially enantioselective synthesis, poses a compelling challenge. Thus, although various synthetic strategies have been devised to construct enantiopure spirocyclic systems, predominantly *via* transition-metal-catalyzed C–H activation and spiroannulation reactions,[6] these approaches, including those for spirosuccinimides[7] and spiropyrroles,[8] have had limited use in the pharmaceutical industry due to their complexity.[9] Nonetheless, the unique structural features of these systems make them promising candidates for exploring novel chemical spaces, particularly in

targeting previously undruggable sites,[10] underscoring the need for simple and efficient synthetic methodologies. These features are commonly observed in multicomponent reactions. In particular, post-Ugi reactions have proven to be a powerful strategy for synthesizing spiro heterocycles, typically through dearomatization processes.[11] Building on our studies of lactams synthesis mediated by radical cyclizations on Ugi adducts derived from arylglyoxals,[12] we have explored the scope of this strategy using benzyl amines derivatives instead of *tert*butylamine ones. Surprisingly, the nature of this component proves to be critical in the chemical outcome, yielding succinimides instead of the expected lactams. Remarkably, starting from enantiopure α-alkylbenzylamines we have achieved, through a chirality transfer process, the diastereoselective synthesis of enantioenriched highly substituted spiro[*2H*-pyrrole-2,3-succinimide] derivatives, structurally unique systems obtained with good yields in one single step draw from Ugi adducts using simple, readily available precursors (Scheme 1).

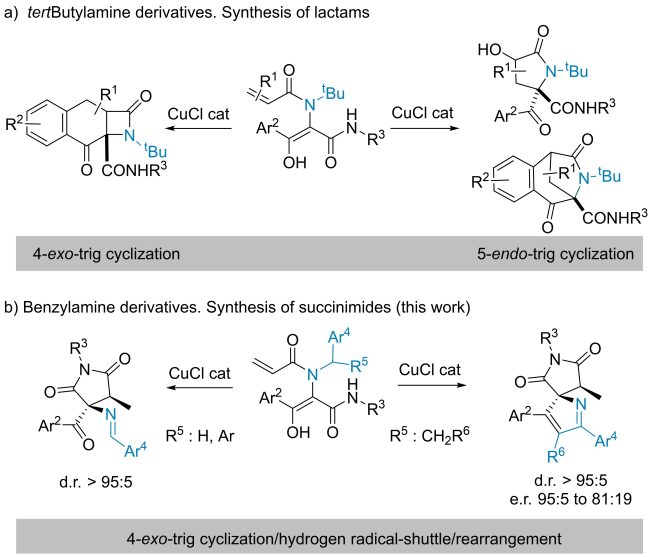
These novel spirocyclic compounds are structurally related to the amathaspiramides, a family of azaspirocyclic marine alkaloids that exhibit antiviral and antimicrobial activities,[13] and whose stereoselective synthesis continues to pose a challenge.[14]

2. Results and Discussion

One-pot diastereoselective synthesis of succinimides substituted by an imine moiety at C3. Building upon our ongoing efforts exploring radical cyclizations of Ugi adducts and the influence of the nature of the amine component,[12] we synthesized the Ugi derivative **1a** from acrylic acid, phenylglyoxal, cyclohexyl isocyanide and benzylamine (see ESI). This Ugi adduct was found to be in its enol form, key for the following copper(I) promoted radical reaction. Interestingly, the treatment of the Ugi adduct **1a** with copper(I) chloride (30 mol%)[15] in boiling dry acetonitrile under an air atmosphere for 18 h led to the unexpected formation of the succinimide **2a** as a single diastereomer bearing an imine substituent in C3 (Table 1, Entry 1). The obtention of the succinimide nucleus instead of the expected azetidinone, resulting from the 4-*exo*-trig cyclization from the peptidyl radical to the acrylamide fragment,[12] can be tentatively attributed to the smaller steric bulk of the benzyl group compared to the *tert*butyl group assayed previously.

With the aim of determining the scope of this methodology, we tried the cyclization on other Ugi derivatives synthesized from different α,β-unsaturated acids, arylglyoxals, isocyanides and benzyl amines, starting from benzyl amines without hydrogen atoms in β position (namely benzylamine, 2-nitrobenzylamine, benzhydrylamine and 1-naphthylmethylamine) (see ESI). Notably, the copper-catalyzed reaction leading to succinimides **2** proved to be general (Table 1), and the X-ray diffraction analysis of a single crystal of succinimide **2e** allowed to confirm both the proposed structure for this family of compounds and their stereochemistry (Figure 1).[16]

We observed how certain factors influence the synthesis of these systems: (1) oxygen is necessary in small amounts, as seen in the synthesis of lactams from *tert*butylamine derivatives,[12] with the optimized conditions involving the use of non-degassed acetonitrile under an inert atmosphere to avoid the oxidative cleavage of Ugi adducts to α-ketoamides[17] (2) the amount of water in the medium is even more critical than the oxygen level, as using wet acetonitrile significantly increases oxidative cleavage and (3) the nature of the isocyanide and the amine is also critical. Thus, the use of bulkier groups improves the synthesis of succinimides, as steric hindrance reduces the formation of imidazolidindione by-products resulting



Scheme 1. One-pot copper(I) promoted radical cyclizations on Ugi adducts derived from arylglyoxals.

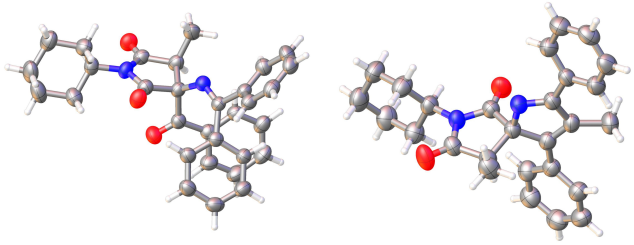
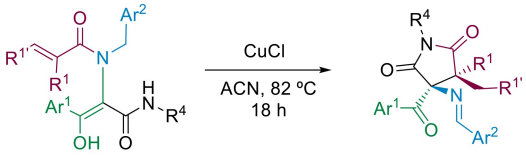


Figure 1. X-ray molecular structure of compounds **2e** and **5f**. The thermal ellipsoid plot (Olex2) is at the 50% probability level.

Table 1. Results of the synthesis of succinimides **2**.[a]

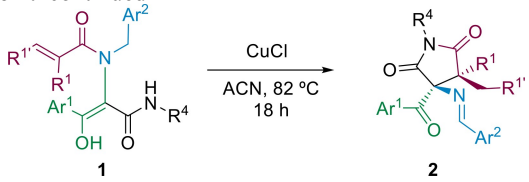


1 **2**

Entry	1	2 (%)[b,c,d]
1	1a $Ar^1 = C_6H_5$, $R^4 = cC_6H_{11}$	2a (49)[e,f]
2	1b $Ar^1 = 4\text{-}FC_6H_4$, $R^4 = cC_6H_{11}$	2b (36)[e,f]
3	1c $Ar^1 = C_6H_5$, $R^4 = tC_4H_9$	2c (47)[e,f]
4	1d	2d (42)[e]
5	1e	2e (31)[e] (70)[g]
6	1f	2 f (44)[e]
7	1 g	2 g (16)[e]
8	1 h	2 h (21)[e]
9	1i	2i (13)[e]

[a] Reaction conditions: **1** (1 mmol), CuCl (30 mol%), dry ACN (20 mL), nitrogen atmosphere, 82 °C, 18 h.
[b] Yield obtained after purification.

Table 1. continued



1 **2**

Entry	1	2 (%)[b,c,d]

[c] In all cases (**2 a-2 h**) only one diastereomer was detected, with (3*R**,4*R**) configuration, except for derivatives **2 g** and **2 h**, where the configuration is (3*R**,4*S**).
[d] Moisture-sensitive compounds.
[e] Purified by column chromatography. Debenzoylation was observed during purification.
[f] Debenzoylated product, **3**, isolated and described (see ESI).
[g] Isolated as solid and purified by re-crystallization.

from the intramolecular *N*-acylation (see Table S3 in ESI).

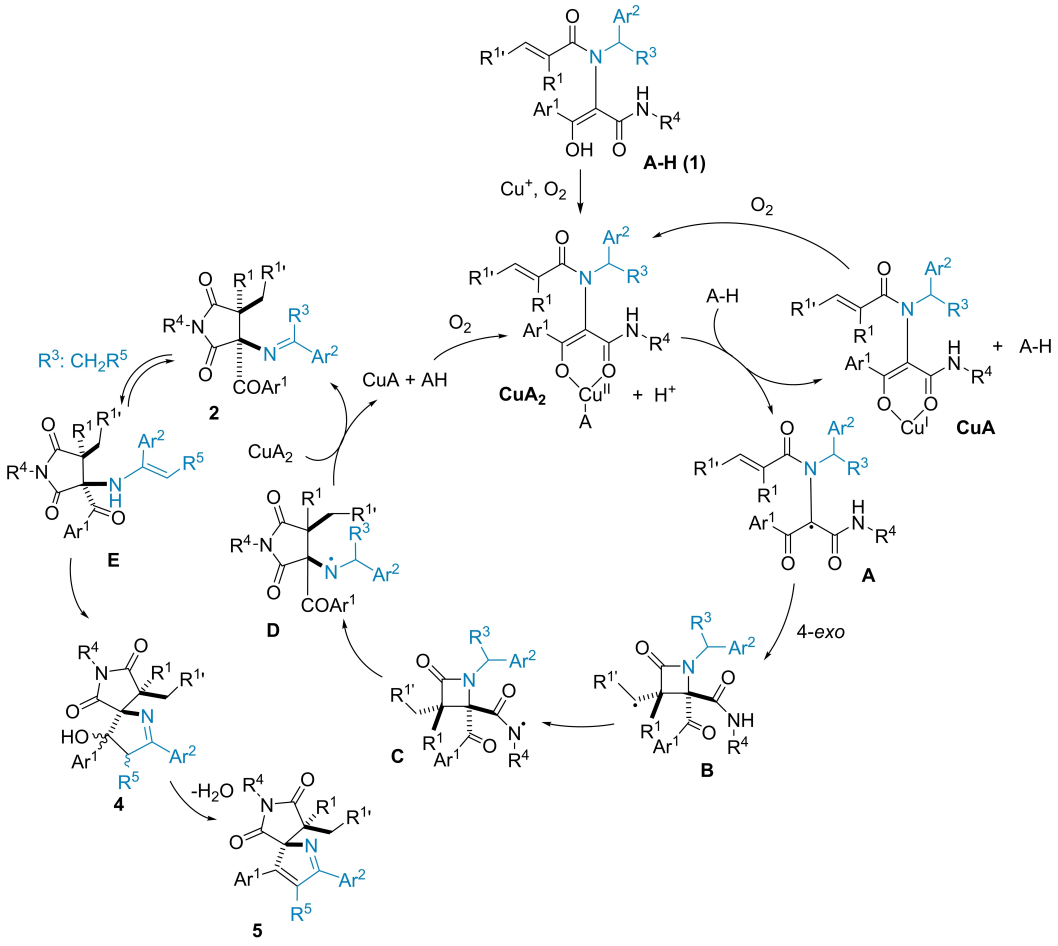
Thus, although the analysis of the reaction mixtures showed complete conversion of the Ugi adducts, the yields of the corresponding succinimides were low to moderate, even under optimized conditions. This can be explained not only by the influence of the substituents in the Ugi adducts but also by the sensitivity of the new compounds to moisture. On one hand, although in most cases the imine group was moderately stable, remaining unchanged after purification of these compounds by column chromatography, the debenzoylated succinimide was quickly generated through a retro-Claisen reaction (see succinimide **3** in ESI). Moreover, in other cases, as in the 5,5-disubstituted succinimides (**2 g-i**) the hydrolysis of the imine group was also quite fast (see Figures S131 and S132 in ESI).

One-pot asymmetric synthesis of spiro[2*H*-pyrrole-2,3-succinimide] derivatives. The synthesis of succinimides functionalized with fairly stable imino groups drawn from benzyl amines, as well as the complete diastereoselectivity observed, prompted us to investigate the potential of this reaction in the construction of more complex systems using chiral α-alkylbenzyl amines, also trying to control the generation of the new stereogenic centers.

In this way, we chose different chiral α-alkylbenzylamines, namely (*R*)-α-methylbenzylamine, (*S*)-α-methyl-4-nitrobenzylamine, (*R*)-α-ethylbenzylamine and (*S*)-1-(1-naphthyl)ethylamine, for the synthesis of Ugi adducts, which were then treated with copper(I) chloride in similar conditions to those described for the synthesis of succinimides **2** (boiling dry acetonitrile under a nitrogen atmosphere for 18 h). Although in this case the reaction only worked with acrylic acid derivatives, the chemical and, above all, stereochemical results obtained for the latter were astonishing. Thus, for the acrylamide Ugi derivatives, treatment with copper(I) salts afforded a mixture of two major

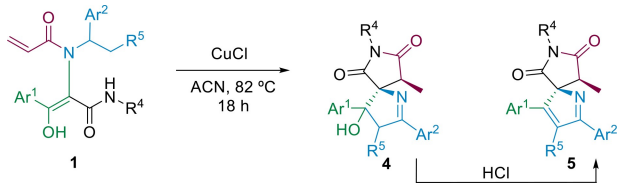
compounds, corresponding to 2-hydroxypyrrolidinspirosuccinimides **4** (as a mixture of two diastereomers) and 2*H*-pyrrolespirosuccinimides **5** (as a single diastereomer). Interestingly, although the diastereoisomers of 2-hydroxypyrrolidinsuccinimides could be isolated by column chromatography (see Table S4 in ESI), treatment of the crude reaction mixture with concentrated hydrochloric acid at room temperature for one hour led, upon dehydration, to the corresponding spiro[*2H*-pyrrole-2,3-succinimide] derivatives **5** as the main product with good chemical yields, complete diastereoselectivity and, moreover, highly enantioenriched (Table 2). The higher yields observed in this synthesis compared with the previous synthesis of succinimides substituted by the imine moiety, can be rationalized by two factors: (1) the use of bulkier amines, which prevents the formation of imidazolidindione by-products, and (2) the rapid tautomerization to enamine, followed by cyclization, which affords stable derivatives. The remarkable stereoselectivity observed could be explained by chirality transfer from the chiral center of the starting amine to the new stereogenic centers in the succinimide, losing the chiral center of the amine in the imine/enamine tautomerization as depicted in Scheme 2 (from **2** to **E**). Furthermore, the absolute configuration of spiro[2*H*-pyrrole-2,3-succinimide] derivatives could be assigned on the basis of the X-ray diffraction analysis of a single crystal of the major isomer of **5 f** (Figure 1).

According to the chemical and stereochemical results, a plausible mechanism accounting for the formation of 2*H*-pyrrolespirosuccinimides **5** can be proposed (Scheme 2). Initially, a Cu(II) complex (CuA_2) would be obtained through a redox reaction involving the Ugi adduct **1** (A–H) in its enol form, a copper(I) salt and oxygen. The peptidyl radical **A** would be generated from this complex along with a Cu(I) complex.[18] A 4-*exo*-trig intramolecular attack on the acrylamide's double bond would drive to intermediate azetidinone radical **B** where the alkyl radical in C3 is on the same face that the benzoyl group in C4, as it was observed in the synthesis of naphthoazetidinones previously described by our group.[12] The proposal of this azetidinone as an intermediate for the synthesis of succinimides is based on the diastereoselectivity observed in the ring



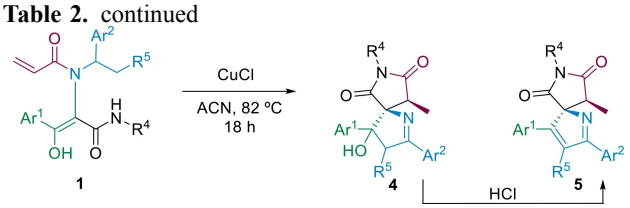
Scheme 2. Proposed mechanism for the synthesis of succinimides **2** and spiro[*2H*-pyrrole-2,3-succinimide] derivatives **5**

Table 2. One-pot stereoselective synthesis of spiro[*2H*-pyrrole-2,3-succinimide] derivatives **5** from Ugi adducts derived from chiral 1-alkylbenzylamines.[a]



Entry	1	5 (%)[b,c]
1	1aa	5a (63) e. r. 91:9[d]
2	1ab	5b (85) e. r. 95:5[d]
3	1ac	5c (32) e. r. 83:17[d]
4	1ad	5d (53) e. r. 91:9
5	1ae	5e (77) e. r. 91:9

Table 2. continued



Entry	1	5 (%)[b,c]
6	1af	5 f (74) e. r. 81:19[d]
7	1ag	5 g (34) e. r. 88:12[d]

[a] Reaction conditions: **1** (1 mmol), CuCl (30 mol%), dry ACN (20 mL), nitrogen atmosphere, 82 °C, 18 h, and subsequent treatment of the crude reaction mixture with concentrated HCl (1 equiv.) at room temperature for 1 hour.
[b] Yield obtained after purification.
[c] In all cases only one diastereomer was detected by ^{1}H NMR spectroscopy (d.r. > 95:5).
[d] Enantiomers ratio was determined by ^{1}H NMR spectroscopy using (*S*)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate as chelating agent solvent (CSA) (see Supporting Information) The absolute configuration was assigned on the basis of the X-ray diffraction structure of **5 f**.

expansion process and the relative configuration achieved, which establishes a correlation between the configurations of both systems. Thus, the cyclization to the azetidinone radical **B** would be followed by a hydrogen atom transfer from the secondary amide to the C-radical, generating an amidyl radical (**C**). The intramolecular attack of this radical to the carbonyl group of the azetidinone, allowed by the medium size of the substituent of the azetidinone nitrogen, would explain the rearrangement to the succinimide radical **D** and the stereochemical outcome, as the attack would take place from the side where the amidyl radical is located, causing the amino radical and alkyl group from the acrylamide fragment to be in a *syn* disposition (see DFT calculations). In the oxidizing conditions of the reaction, the resulting amino radical (**D**) would evolve to the isolated imines (**2**). The incorporation of α-alkyl substituents in the benzyl amine component would allow the tautomerization to enamine, leading to the isolated aldol products **4** and, then, to the corresponding dehydrated pyrrolespirosuccinimide **5**.

Theoretical calculations. Further insights into the reaction mechanism were obtained by DFT calculations at the B3LYP/6-31G(d,p) level in the gas phase.[19] In this way the most intriguing steps were studied, that is, the conversion from the azetidinone intermediate **B** to the succinimide intermediate **D**.

Initially, we optimized the geometries of the proposed intermediates **B**, **C** and **D** in the synthesis of **2 a**. Thus, although the *C*-centered azetidinone radical **B** is more stable than the *N*-centered azetidinone radical **C**, the succinimide *N*-radical **D** is far more stable than any of them. However, despite the chair-like transition state found in the proposed 1,5-HAT process for the conversion of **B** to **C**, the calculations show a high free energy of activation for this step (32.6 kcal mol^{-1}) which prevents the hydrogen transfer process even in boiling acetonitrile, with a calculated reaction rate at 82 °C of $k_1 = 6.4 \times 10^{-8}$ s^{-1}.[20] This high barrier could be explained by the observed distortion in the azetidinone ring during the hydrogen transfer process. However, the lower barrier for the expansion from the *N*-centered azetidinone radical **C** to the succinimide radical intermediate **D** (22.0 kcal mol^{-1}) would allow the rearrangement reaction in refluxing acetonitrile ($k_2 = 2.1 \times 10^{-1}$ s^{-1}) (Figure 2.a).

With the aim of explaining the hydrogen transfer from **B** to **C** we proposed an underexplored hydrogen radical-shuttle (HRS) process,[21] with the enolic Ugi adduct acting as both shuttle and hydrogen source. In order to reduce computational expenses, a simplified model where the cyclohexyl and benzyl substituents on the amide groups of the azetidinone were trimmed to methyl groups, and only the β-ketoamide in the Ugi adduct was considered. First, the energy of activation for the 1,5-HAT process in the new model was calculated to allow meaningful comparisons with the energy calculated for the HRS process (Figure 2.b). The results demonstrate that this energy remained high despite the less sterically hindered substituents. Thus, the calculated barrier for the 1,5-HAT process (36.0 kcal mol^{-1}) disfavors the hydrogen transfer process in refluxing acetonitrile ($k_1 = 4.8 \times 10^{-10}$ s^{-1}). In this way, we calculated the energy for the proposed radical-shuttle process, finding a plausible two-step process where the enol acted as a shuttle, first as a hydrogen source for the C-radical (20.9 kcal mol^{-1}, $k_1 = 1.0$ s^{-1} in boiling acetonitrile), and then as a hydrogen acceptor from the NH site (21.2 kcal mol^{-1}, $k_2 = 0.7$ s^{-1} in boiling acetonitrile) (Figure 2.c). Thus, although much less explored, the computational studies support a hydrogen radical-shuttle mechanism as a key step in the synthesis of succinimides.

3. Conclusion

In this work, we demonstrate the potential of copper-catalyzed post-Ugi reactions in constructing highly substituted complex heterocycles. The use of enantio-

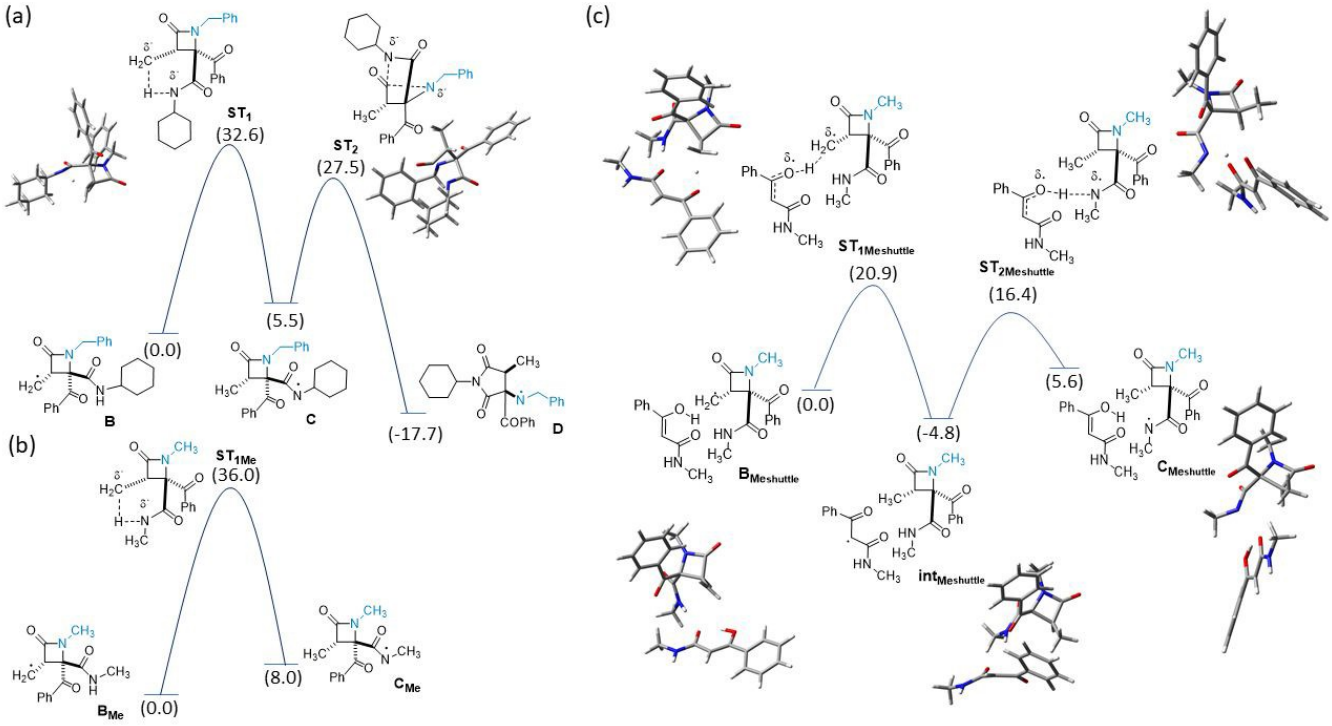


Figure 2. Energy diagrams for the proposed **B-C** and **C–D** transformations. (a) Energy diagram for the conversion of **B** to **D** in the synthesis of **2 a** through a 1,5-HAT/expansion sequence. (b) Energy diagram for the conversion of **B** to **C** through a 1,5-HAT process in a simplified system. (c) Energy diagram for the conversion of **B** to **C** through an HRS process in a simplified system. The reported free energy values are in kcal mol^{-1} and refer to calculations performed in gas phase.

pure α-alkylbenzyl amines and arylglyoxals as starting reagents in the Ugi reaction has enabled the synthesis of previously undescribed spiro-*2H*-pyrrole-2,3-succinimides with complete diastereoselectivity and high enantiomeric purity in just two steps, via a chirality transfer process. The isolation of intermediates such as *N*-succinimidyl imines or the previously reported azetidinones, combined with the stereochemical outcomes and the DFT calculations, supports a proposed mechanism in which a largely unexplored hydrogen radical-shuttle process plays a crucial role.

Experimental Section

General Procedure for the Synthesis of Ugi Adducts 1

Arylglyoxal hydrate (2 mmol, 1 equiv.) was dissolved in methanol, after which the corresponding benzyl amine (2 mmol, 1 equiv.), carboxylic acid (2 mmol, 1 equiv.) and isocyanide (2 mmol, 1 equiv.) were added. The corresponding mixture was stirred at room temperature for 24 hours. When a solid was obtained, the precipitate was isolated by vacuum filtration, washed with cold methanol and dried *in vacuo*. When no precipitate was observed a 1 M hydrochloric acid aqueous solution was added to the solution. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane. This solution was washed with a 1 M hydrochloric acid aqueous solution and a saturated sodium carbonate aqueous solution. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The product was purified by flash column chromatography (SiO_2, hexane/ethyl acetate).

General Procedure for the Synthesis of 3-Benzylideneaminosuccinimides 2

Copper(I) chloride (0.3 mmol, 0.3 equiv.) and the corresponding Ugi adduct (1 mmol, 1 equiv.) were placed in a round-bottom flask. The reagents were dissolved in dry acetonitrile and the reaction mixture was heated to reflux with a heating block for 18 hours under nitrogen, after which the solvent was removed in a rotary evaporator. The residue was dissolved in ethyl acetate (30 mL) and the corresponding solution was washed with a 1 M hydrochloric acid aqueous solution and a saturated sodium carbonate aqueous solution. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. Products were purified by flash column chromatography (SiO_2, hexane/ethyl acetate) or recrystallization.

General Procedure for the Synthesis of Pyrrolespirosuccinimides 5

Copper(I) chloride (0.3 mmol, 0.3 equiv.) and the corresponding Ugi adduct (1 mmol, 1 equiv.) were placed in a round-bottom flask. The reagents were dissolved in dry acetonitrile and the reaction mixture was heated to reflux with a heating block for 18 hours under nitrogen, after which the solvent was removed in a rotary evaporator. The residue was dissolved in ethanol and treated with hydrochloric acid (37 %, 1 equiv) at room temperature for 1 h. Ethanol was then removed and water was added. The aqueous phase was extracted with dichloromethane. The organic phase was washed with water and dried over anhydrous sodium sulfate, filtered and concentrated to dryness. Products were purified by flash column chromatography (SiO_2, hexane/ethyl acetate).

Computational Details

The geometries of all species were fully optimized at the B3LYP/6-31G(d,p) level in the gas phase. The nature of all optimized structures was determined using harmonic frequency analysis as true minima with no imaginary frequencies, or transition states with only one imaginary frequency. All transition-state structures and reaction paths were further validated by intrinsic reaction coordinate (IRC) calculations in both forward and reverse directions. All reported energies correspond to free Gibbs energies. All calculations were performed using the Gaussian 16 program.[18]

Acknowledgements

We thank funding from MICIU/AEI/10.13039/501100011033 and ERDF, UE (grants PID2020-117610RB–I00 and PID2023-151848OB–I00) and Consejería de Educación de la Junta de Castilla y León and ERDF, UE (Project BU067P20). J. G.-A. thanks Consejería de Educación de la Junta de Castilla y León and ERDF, UE for his predoctoral and post-doctoral contracts.

References

[1] a) M. M. Heravi, V. Zadsirjan, *RSC Adv.* **2020**, *10*, 44247–44311; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274; c) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.

[2] Z. Zhao, J. Yue, X. Ji, M. Nian, K. Kang, H. Qiao, X. Zheng, *Bioorg. Chem.* **2021**, *108*, 104557.

[3] a) B. H. Ganesh, A. G. Raj, B. Aruchamy, P. Nanjan, C. Drago, P. Ramani, *ChemMedChem* **2024**, *19*, e202300447; b) S.-M. Choi, J. H. Kim, *Adv. Synth. Catal.* **2024**, *366*, 2–17; c) E. Mateev, M. Georgieva, A. Zlatkov, *J. Pharm. Pharm. Sci.* **2022**, *25*, 24–40; d) G. L. Petri, V. Spanò, R. Spatola, R. Holl, M. V. Raimondi, P. Barraja, A. Montalbano, *Eur. J. Med. Chem.* **2020**, *208*, 112783; e) M. Y. Belikov, O. V. Ershov, *Chem. Heterocycl. Compd.* **2016**, *52*, 279–281; f) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma, *RSC Adv.* **2015**, *5*, 15233–15266.

[4] Spiro compounds. Synthesis and applications. Ed. R. Rios-Torres, **2022**, Wiley.

[5] a) K. Hiesinger, D. Dar'in, E. Proschak, M. Krasavin, *J. Med. Chem.* **2021**, *64*, 150–183; b) D. Bora, A. Kaushal, N. Shankaraiah, *Eur. J. Med. Chem.* **2021**, *215*, 113263.

[6] Q. Zhou, B. Li, X. Zhang, X. Fan, *Org. Biomol. Chem.* **2024**, *22*, 2324–2338.

[7] a) E. Kamaraj, P. Roy, Y. R. Lee, *Adv. Synth. Catal.* **2023**, *365*, 3915–3926; b) A. Skhiri, A. Taborosi, N.

Ohara, Y. Ano, S. Mori, N. Chatani, *Org. Chem. Front.* **2023**, *10*, 1617–1625; c) E. Chung, S. Kim, A. Rakshit, P. Singh, J. Park, T. Jeong, I. S. Kim, *J. Org. Chem.* **2023**, *88*, 11227–11239; d) A. Dutta, M. Jeganmohan, *Org. Lett.* **2023**, *25*, 6305–6310; e) C. Sen, B. Sarvaiya, S. Sarkar, S. C. Ghosh, *J. Org. Chem.* **2020**, *85*, 15287–15304; f) B. Ramesh, M. Tamizmani, M. Jeganmohan, *J. Org. Chem.* **2019**, *84*, 4058–4071.

[8] C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2014**, *47*, 2558–2573.

[9] A. Ding, M. Meazza, H. Guo, J. W. Yang, R. Rios, *Chem. Soc. Rev.* **2018**, *47*, 5946–5996.

[10] S. Dandapani, L. A. Marcaurelle, *Nat. Chem. Biol.* **2010**, *6*, 861–863.

[11] a) X. Tang, Q. Tao, L. Song, E. V. Van der Eycken, *Org. Chem. Front.* **2024**, *11*, 4895–4912; b) X. Tang, L. Song, E. V. Van der Eycken, *Chem. Rec.* **2023**, *23*, e202300095; c) L. Song, C. Liu, G. Tian, L. Van Meervelt, J. Van der Eycken, E. V. Van der Eycken, *Mol. Catal.* **2022**, *522*, 112240.

[12] J. Gómez-Ayuso, M. Lezcano, I. Carreira-Barral, B. González-Saiz, R. Quesada, M. García-Valverde, *Adv. Synth. Catal.* **2023**, *365*, 3658–3665.

[13] B. D. Morris, M. R. Prinsep, *J. Nat. Prod.* **1999**, *62*, 688–693.

[14] a) Z. He, L. Peng, C. Guo, *Nature Synth.* **2022**, *1*, 393–400; b) M. O'Connor, C. Sun, D. Lee, *Angew. Chem. Int. Ed.* **2015**, *54*, 9963–9966.

[15] Although succinimides were also obtained by reducing the CuCl amount to 10 mol%, a slight decrease in chemical yield was observed.

[16] CCDC-2404747 (for **2h**) and 2404748 (for **5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

[17] A. Ghoshal, M. D. Ambule, R. Sravanthi, M. Taneja, A. K. Srivastava, *New. J. Chem.* **2019**, *43*, 14459–14474.

[18] P. Garra, F. Dumur, M. Nechab, F. Morlet-Savary, C. Dietlin, B. Graff, E. P. Doronina, V. F. Sidorkin, D. Gigmes, J.-P. Fouassier, J. Lalevée, *Macromolecules* **2018**, *51*, 6395–6404.

[19] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M., Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, Williams, F., Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E., Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P., Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O., Farkas, J. B. Foresman, D. J. Fox, Gaussian 16 Rev. C.01, Wallingford, CT, **2016**.

[20] Reaction rate of reactions calculated using the Eyring-Polanyi equation.

[21] B. Yang, S.-J. Li, Y. Wang, Y. Lan, S. Zhu, *Nat. Commun.* **2021**, *12*, 5257.

RESEARCH ARTICLE

Asymmetric Synthesis of Highly Substituted Spiro[*2H*-pyrrole-2,3-Succinimide] Derivatives by Copper-Catalyzed Post-Ugi Reactions

Adv. Synth. Catal. **2025**, *367*, e202500166 (1 of 8)

J. Gómez-Ayuso, I. Carreira-Barral, R. Quesada, M. García-Valverde*