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Novel spirocyclic scaffold accessed *via* tandem Claisen rearrangement – intramolecular Michael addition

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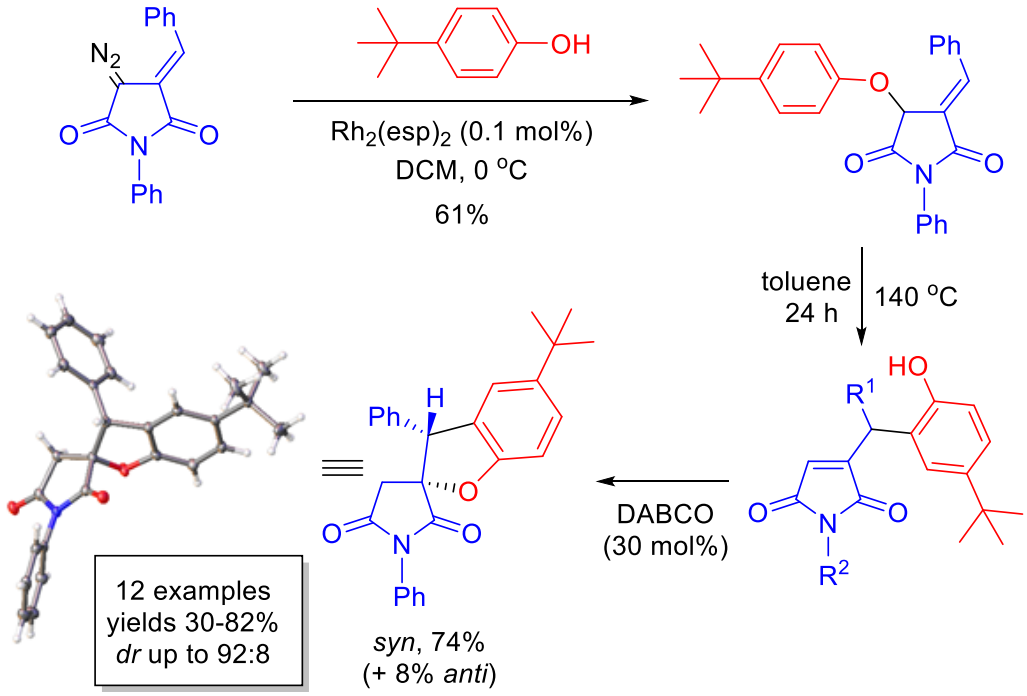


Keywords: rhodium(II) carbene O-H insertion; diazo arylidene succinimides; Claisen rearrangement; intramolecular Michael addition; spirocycles.

Abstract

A straightforward access to novel spiro[benzofuran-2,3'-pyrrolidine]-2',5'-diones based on $Rh_2(esp)_2$-catalyzed insertion of carbenes derived from diazo arylidene succinimides (DAS) into O-H bond of phenols is described. The initial adducts underwent a thermally promoted Claisen rearrangement followed by DABCO-catalyzed intramolecular 5-*exo*-*dig* Michael addition.

Introduction

Spirocycles undoubtedly occupy a special place in drug design [1] and, in general, spirocyclic compounds intended for the interrogation of biological targets have been associated with higher success rates [2] in discovering new cases of affinity towards a three-dimensional protein molecule [3]. Spirocycles of all sorts are omnipresent in the natural product realm [4]. Among the approved medicines the following spirocyclic molecules are notable: spironolactone for heart disease and hypertention [5], buspirone for anxiety disorders [6], cevimeline for dry mouth and dry eye syndrome [7], fluspirilene for schizophrenia [8] and ilbesartan for hypertention and diabetic nephropathy [9], to mention a few (Figure 1).

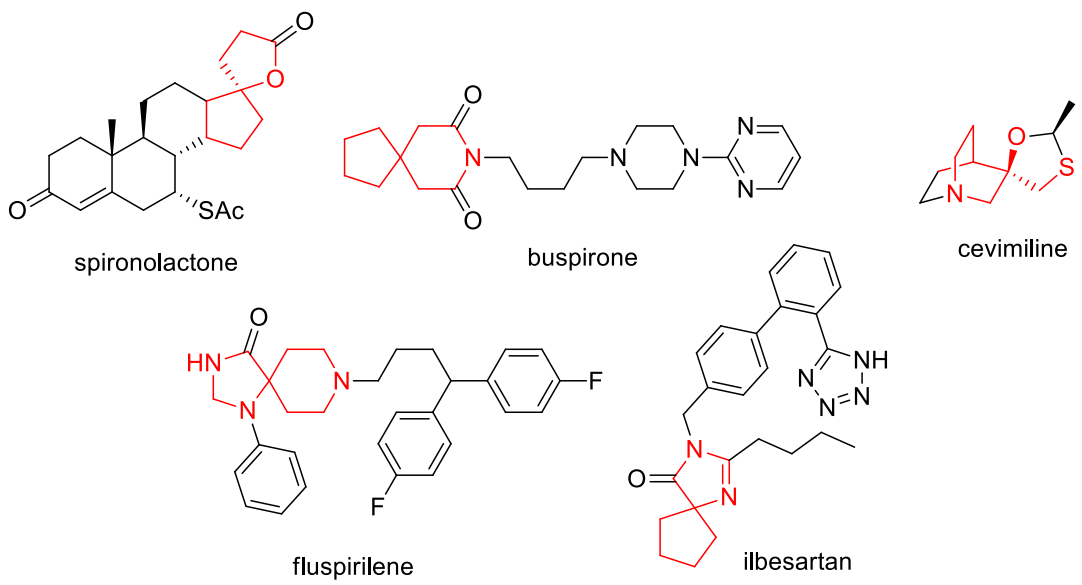
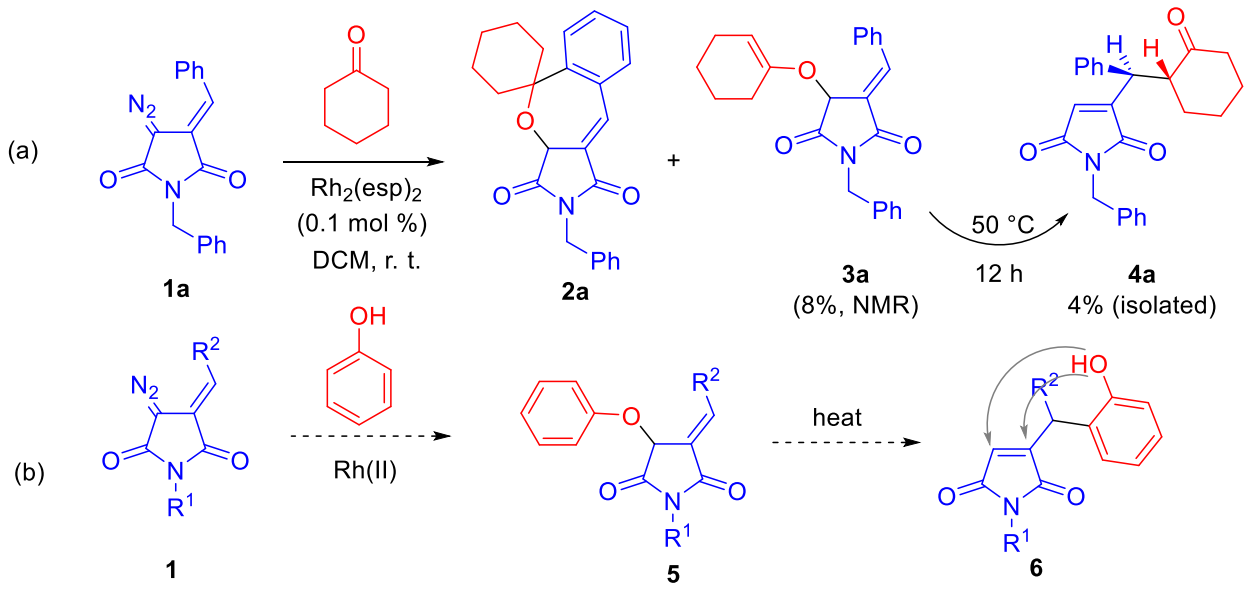


Figure 1. Examples of approved spirocyclic drugs.

Hence the development of novel synthetic methods to construct spirocycles constitutes a distinctly worthy undertaking which may as well influence the outlook of the novel medicines discovered and developed in the future.

Recently, we described a novel Rh(II)-catalyzed spirocyclizations involving diazo arylidene succinimide (DAS, such as **1a**) with cyclohexanone (as well as other cyclic ketones) which delivered spiro-annulated 2-benzoxepines (such as **2a**) along with a minor by-product **3a** identified by ^{1}H NMR as the product of formal insertion of the rhodium(II) carbene species into the O-H bond of cyclohexanone enol form. This minor by-product, on heating at 50 °C for 12 h, underwent the Claisen rearrangement to give diastereomerically pure maleimide **4a** in 4% yield [10]. While for our study at the time the formation of **3** and **4** were viewed as a minor side-reaction, later be started pondering the possibility of giving the observed transformation a stronger impetus from the synthetic point of view. Specifically, we wanted to see if Rh(II)-

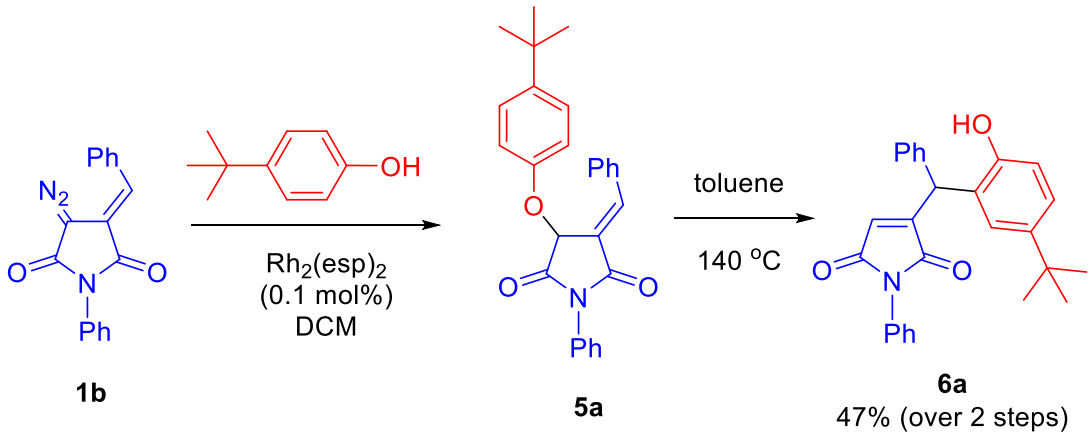
catalyzed insertion of DAS-derived carbenes could be performed into the O-H bong of phenols and if the resulting phenoxy-substituted succinimides **5** could also undergo a Claisen rearrangement. The products of the latter (**6**) would again have a reactive phenolic hydroxy group which could potentially be involved in post-condensational transformations such as intramolecular oxa-Michael addition (Scheme 1). Herein, we report our findings obtained in the course of investigating the viability of this strategy.



Scheme 1. (a) Earlier reported Rh(II)-catalyzed spirocyclization of DAS with the formation of minor enol ether product **2** and its Claisen rearrangement; (b) Synthetic strategy investigated in this work.

Results and Discussion

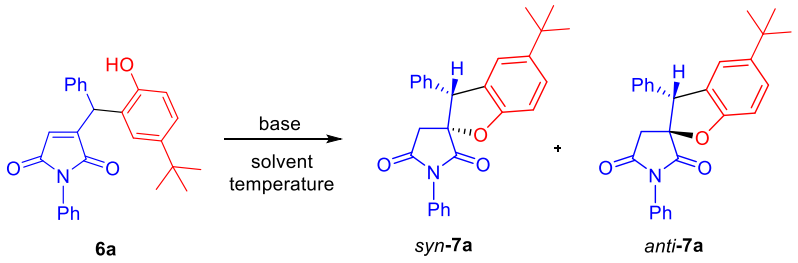
The initial attempt to involve DAS **1b** in the $Rh_2(esp)_2$-catalyzed insertion reaction with 4-(*tert*-butyl)phenol was successful. The initial adduct **5b** was not purified and was heated at 140 °C in toluene to give compound **6b** in 47% yield over two steps (Scheme 2). No further optimization of the reaction conditions was undertaken except for the isolation for the initial O-H insertion product which facilitated subsequent steps (the Claisen rearrangement and the final cyclization, *vide infra*).



Scheme 2. Initial attempt at Rh(II)-catalyzed O-H insertion/Claisen rearrangement.

With product **6a** at hand we proceeded studying its base-promoted Michael-type cyclizations. As it follows from the data collated in Table 1, to our delight, cyclizations of the phenoxide anion generated on the action of base (except for 2,6-lutidine) proceeded as 5-*exo-dig* (rather than 6-*endo-dig*) process and yielded spirocyclic compound **7a** as a mixture of *syn* and *anti* diastereomers. DABCO in toluene at room temperature over 1 h (entry 5) gave a superior result both in terms of the isolated yield and diastereoselectivity. Increasing the polarity of the solvent appeared to be detrimental to the reaction outcome.

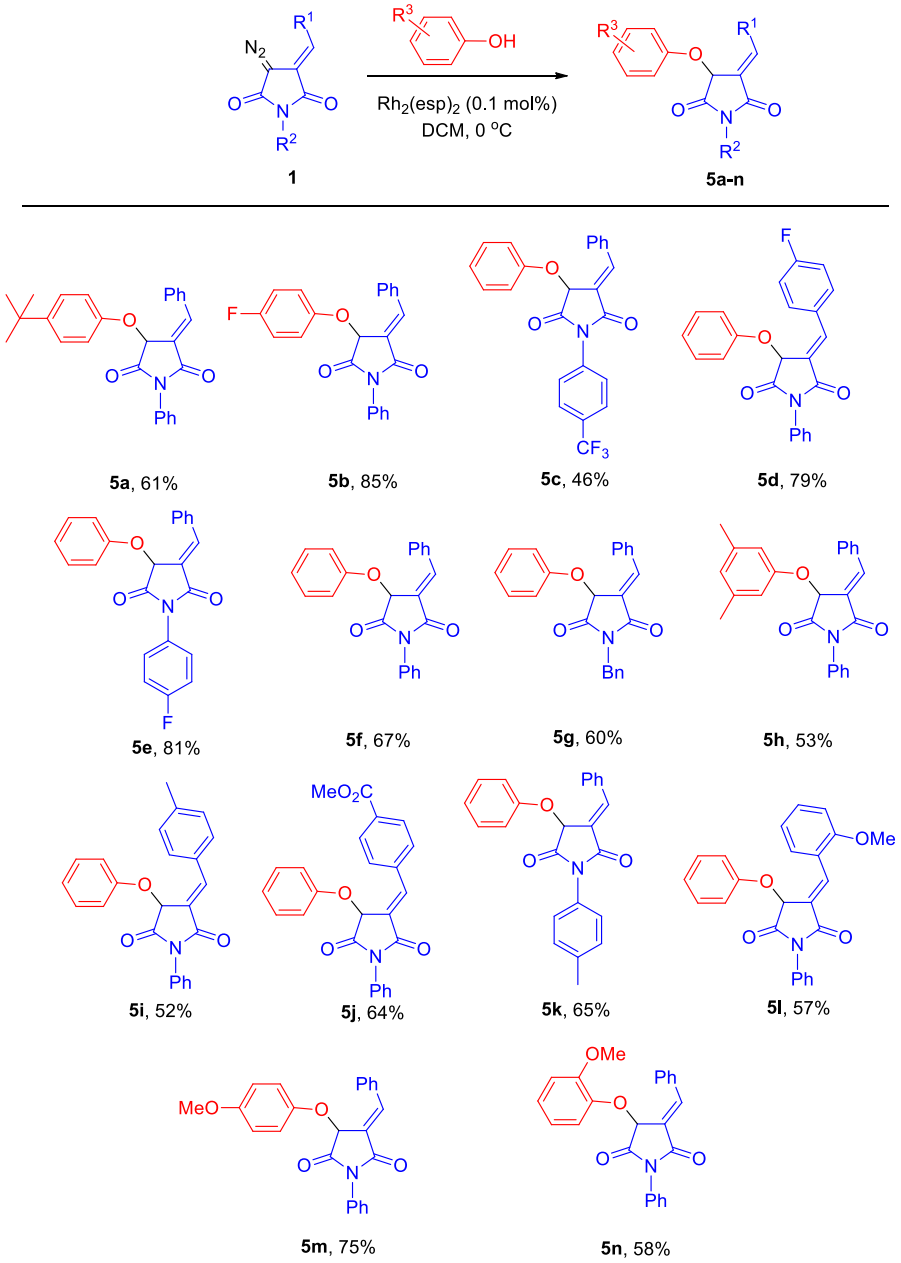
Table 1. Investigation of base-catalyzed transformation of compound **6a**.



Entry	Solvent	Base (30 mol.%)	T (°C)	Total yield (%)	*syn/anti*	Conversion within 1 h (%)
1	Toluene	DABCO	0	34	79:21	70
2	Toluene	DBU	25	63	62:38	100
3	Toluene	Cs_2CO_3	25	66	73:27	100
4	Toluene	2,6-lutidine	25	–	–	–
5	Toluene	DABCO	25	**71**	**81:19**	100
6	acetonitrile	DABCO	25	66	77:23	100
7	Methanol	DABCO	25	48	46:54	100
8	MeOH:H_2O (1:1)	DABCO	25	–	–	–

With the conditions identified for the $Rh_2(esp)_2$-catalyzed insertion into phenolic O-H bond, Claisen rearrangement and base-catalyzed cyclization into spirocyclic product, we experimented with attempts to perform all three steps in a one-pot format. This gave inferior result in terms of product yield and purity. The best result was obtained by performing the Rh(II)-catalyzed insertion first, purifying the respective product **5** – and then engaging it in sequential Claisen rearrangement – cyclization reactions performed in one-pot format.

To expand the scope of the newly discovered transformations, several products of the Rh(II)-catalyzed O-H insertions **5** were synthesized as detailed in Scheme 3.



Scheme 3. $Rh_2(esp)_2$-catalyzed O-H insertion reactions between various DAS **1** and phenols.

The O-H insertion reaction worked well for electron-neutral or electron-rich phenols. The presence of electron-withdrawing substituents (such as 4-Cl or 2,4-diCl) in the phenol component drastically diminished the yield and led to the formation of the earlier reported DAS dimer [11]. Similarly, electron-donating groups (such as 4-methnoxy) in the arylidene portion of **1** complicated the course of the reaction.

Having amassed a sizable arsenal of O-H insertion products **5a-n**, we proceeded to study their behavior in the two-step, one-pot sequence of the Claisen rearrangement/intramolecular Michael-type spirocyclization as detailed in Scheme 4. In two cases (**7a** and **7c**), the major (*syn*) and minor (*anti*) diastereomers were separated chromatographically and characterized. In one case (**7a**), the structure of the major (*syn*) diastereomer was unequivocally confirmed by single-crystal X-ray crystallography. In all other cases, only pure *syn* diastereomer was isolated and characterized. The yields of spirocyclic products were generally modest to good over two steps. Electron-accepting group in the benzylidene portion (**5j**) or *N*-benzyl substitution in the starting material (**5g**) lowered the reactivity and the Claisen rearrangement step was performed at a higher (150 °C) temperature.

Notable was our inability to involve *o*-methoxy- (**5n**) and (*p*-methoxy)phenoxy (**5m**) substrates in the two-step synthesis of the respective spirocycles **7**. In both cases, ^{1}H NMR analysis of the reaction mixture indicated the formation of complex product mixtures at the Claisen rearrangement step.

3,5-Dimethylphenoxy-substituted substrate **5h** gave the best diastereomeric ratio in the series. The preference for the formation of the *syn* diastereomer in each case (and for **5a→7a** in particular) can, in principle, be rationalized by the greater steric repulsion in the conformer of the respective oxyanion leading to *anti* diastereomer compared to that from which the major, *syn* diastereomer is formed (Figure 2).

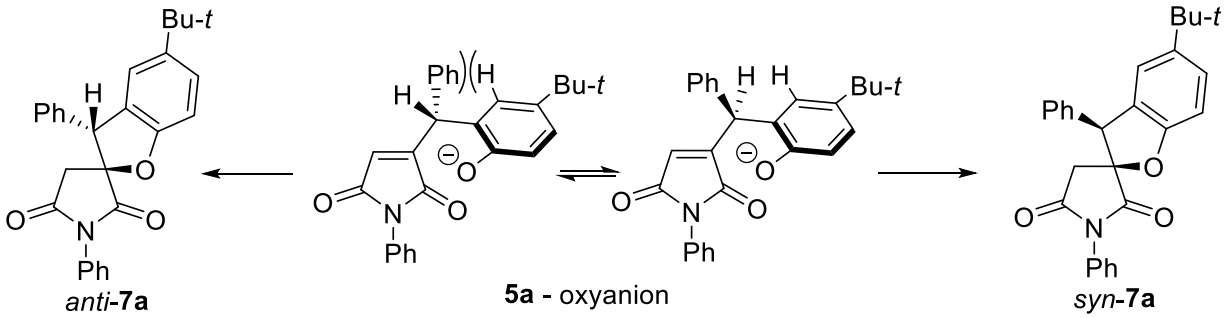
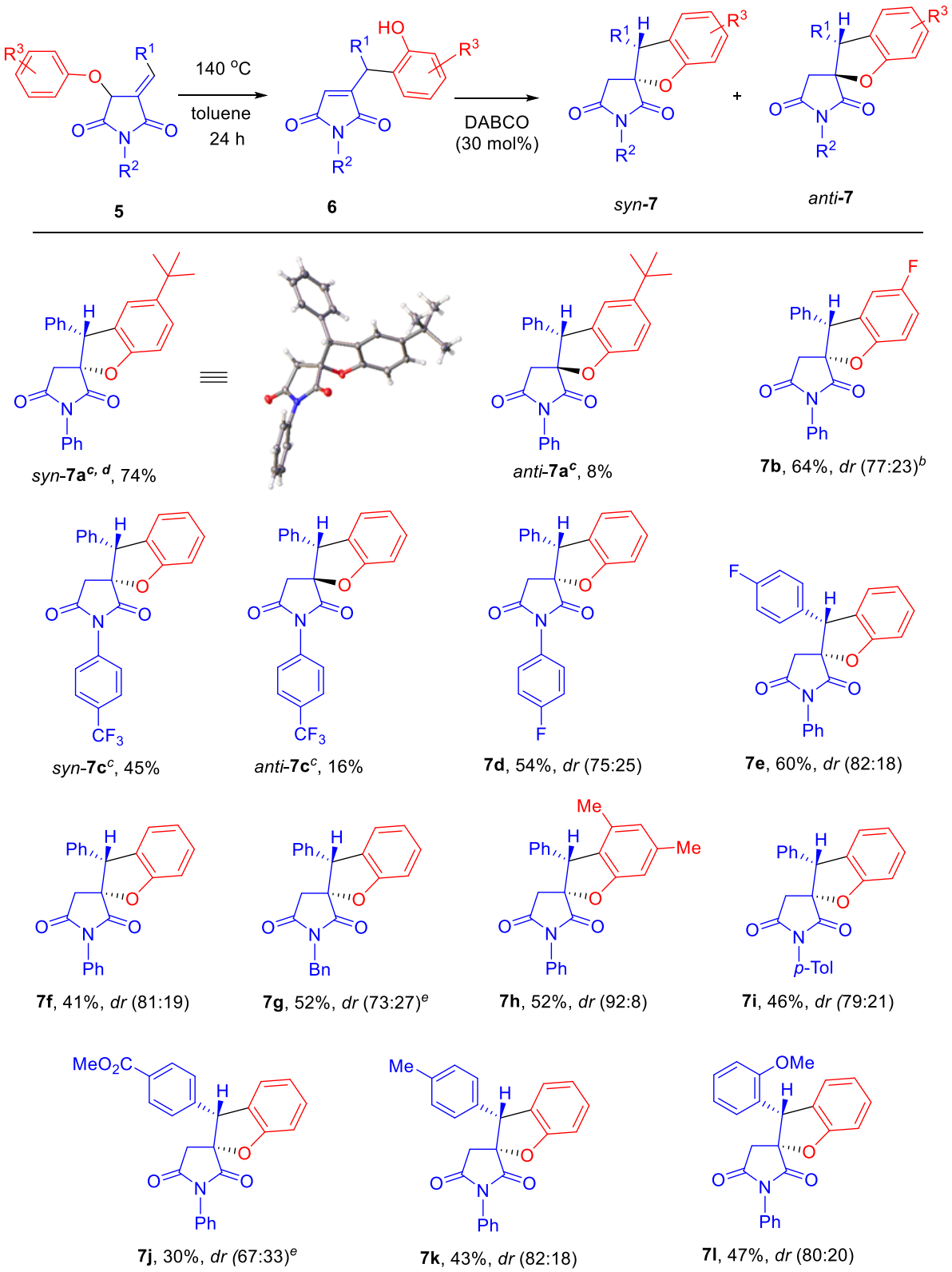


Figure 2. Tentative rationalization of the diastereoselectivity observed in all **5→7** transformations (shown for **5a→7a**).



Scheme 4. Two-step, one-pot sequence of the Claisen rearrangement/intramolecular Michael-type spirocyclization of substrates **5a-n**. [a] The Claisen rearrangement product was not isolated; Scale from 0.3 to 0.9 mmol; pure major *syn* diastereomer was isolated and characterized in all cases; [b] *syn/anti* ratio is shown in parentheses; [c] In these examples, pure minor *anti* diastereomer was isolated and characterized; [d] The structure was confirmed by crystallography. [e] The reaction was performed at 150 °C.

Notably, compound analogous to **5a** was synthesized with thiophenol in 78% yield. However, it turned out to be completely unreactive towards the Claisen rearrangement step, even at 150 °C in 1,2-dichlorobenzene. Raising the temperature to 200 °C led to starting material deterioration and was not productive either.

Spirocyclic products **7a-l** were tested for their ability to influence the survival of MDA-MB-231 (breast adenocarcinoma) and NCI-H460 (lung cancer) cell lines and proved completely non-cytotoxic. This validates these new compounds as suitable molecular probes for interrogating various biological targets *via* screening in cell-based assays.

Conclusion

We have developed a straightforward access to novel spiro[benzofuran-2,3'-pyrrolidine]-2',5'-diones based on $Rh_2(esp)_2$-catalyzed insertion of carbenes derived from α-diazosuccinimides (DAS) into O-H bond of phenols. The initial adducts underwent a thermally promoted Claisen rearrangement followed by DABCO-catalyzed intramolecular 5-*exo*-*dig* Michael addition. The resulting spirocyclic compounds are formed with a clear preference to the *syn* diastereomer over *anti* which can be rationalized by conformational analysis of the Claisen rearrangement precursors to their formation.

Deposition Number 2166113 (for *syn*-**7a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information

Supporting Information File 1

General experimental information, X-ray crystallographic data, synthetic procedures, analytical data and NMR spectra for the reported compounds.

[https://www.beilstein-journals.org/bjoc/content/supplementaryxxxx-xxxx-xx-xx-S1.pdf]

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