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Enantioselective Synthesis of Pyrrolizidinone Scaffolds through Multiple-Relay Catalysis

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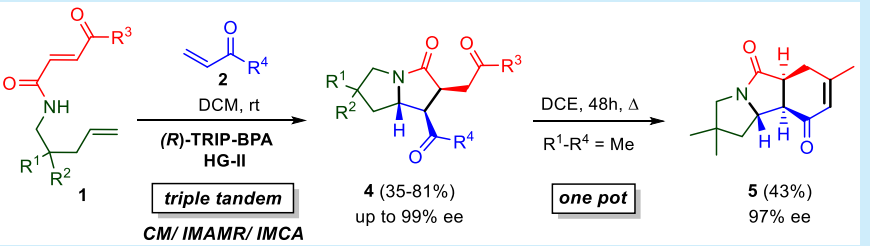

ABSTRACT: A triple-tandem protocol for the synthesis of the pyrrolizidinone skeleton has been devised. It involves a cross metathesis−intramolecular aza-Michael reaction−intramolecular Michael addition tandem sequence, starting from *N*-pentenyl-4-oxo-2-alkenamides and conjugated ketones. In the presence of two cooperative catalysts, namely the second-generation Hoveyda−Grubbs catalyst and (*R*)-TRIP-derived BINOL phosphoric acid, this multiple-relay catalytic process takes place in good yields and outstanding levels of diastero- and enantioselectivity with the simultaneous generation of three contiguous stereocenters

The pyrrolizidine skeleton, an azabicycle with two aliphatic five-membered rings and a nitrogen atom at the bridgehead position, is a structural motif present in a wide variety of natural products. The number of pyrrolizidine-containing alkaloid species reaches up to 6000, most of which are hepatotoxic secondary metabolites synthesized by plants.[1] Specifically, the pyrrolizidinone subunit deserves a special mention as recently isolated pyrrolizidinone-containing compounds display a wide range of biological activities. In this context, compound CJ-16,264 (Figure 1, **A**)[2] and penibruguieramine A (Figure 1, **B**)[3] exhibit potent antibacterial properties, while UCS1025A is a strong inhibitor of telomerase (Figure 1, **C**).[4] One of the simplest pyrrolizidinone derivatives, pyrrolam A (Figure 1, **D**), presents herbicidal activity,[5] whereas conjugation with a sugar provides the antifungal properties of burnettramic acids (Figure 1, **E**).[6] Compound **F** (Figure 1) is a highly potent second-generation phosphodiesterase IVb inhibitor and a candidate for the treatment of asthma.[7] Due to its great biological relevance, multiple synthetic efforts have been devoted to the synthesis of highly functionalized pyrrolizidinone derivatives, and several approaches have been established.[8] However, these small bicyclic ring systems turned out to be challenging targets for synthetic chemists, especially in an asymmetric manner. Chiral-pool and chiral-auxiliary strategies are the most common approaches for the asymmetric synthesis of these derivatives. The use of catalytic enantioselective methodologies is scarce, and most of them involve enantioselective [3 + 2] dipolar cycloadditions for the generation of the bicyclic structure.[9] Therefore, the development of efficient and general enantioselective approaches to access these relatively simple scaffolds remains a challenge.

On the other hand, domino or tandem reactions entail two or more bond-forming reaction steps occurring in a single

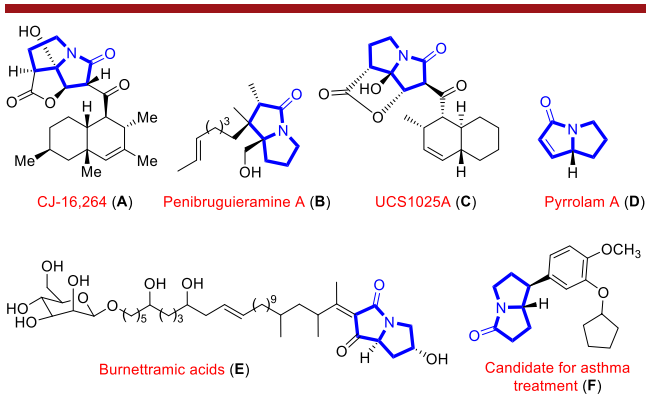

Figure 1. Biologically active pyrrolizidinone-derived compounds.

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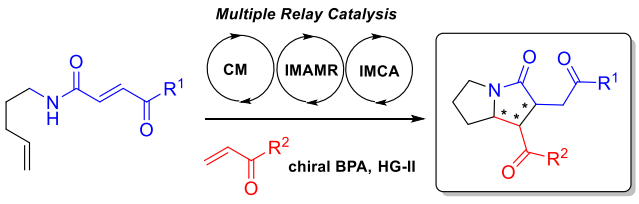
operation under the same reaction conditions. The combination of domino reactions and asymmetric catalysis results in a simple and effective way to create multiple stereocenters. Thus, the field of enantioselective tandem catalysis has witnessed tremendous progress in recent years.[10]

The simultaneous use of several catalysts with different modes of action (multicatalysis) is one of the most fruitful strategies to design new domino processes, enabling unprecedented transformations not accessible using each catalyst separately. In this context, the combination of transition metal catalysts and organocatalysts has emerged as a powerful strategy, thereby creating novel concepts within catalysis.[11]

One of the main challenges in the design of multicatalytic processes is related to ensuring the compatibility of the catalysts. Chiral Brønsted acids are suitable catalysts for domino and multicomponent reactions as they have shown to be compatible with several catalysts, both metal catalysts and organocatalysts.[12] Among those combinations, the combination of a chiral BINOL phosphoric acid (BPA) with a metal catalyst has found a wide range of applications in organic synthesis.[13]

Herein we report another example of the synergistic combination of a chiral BPA with the second generation Hoveyda–Grubbs catalyst (**HG-II**) in a triple-tandem process. The reaction of *N*-(4-pentenyl)-4-oxo-2-alkenamides with conjugated ketones in the presence of a chiral BPA and **HG-II** afforded enantiomerically enriched pyrrolizidinones with the simultaneous generation of three contiguous stereocenters. The formation of these compounds involves an unprecedented multiple-relay catalytic process, which comprises a tandem cross metathesis–intramolecular aza-Michael addition–intramolecular conjugated addition strategy (Scheme 1).

Scheme 1. Tripe-Tandem Strategy to Access Chiral Pyrrolizidinone Derivatives



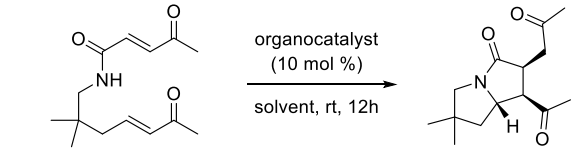
CM = cross-metathesis
IMAMR = intramolecular aza-Michael reaction
IMCA = intramolecular conjugated addition

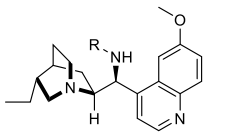
Our initial aim was the evaluation of a novel organocatalytic tandem intramolecular aza-Michael reaction (IMAMR)–intramolecular conjugated addition (IMCA) protocol. The participation of intramolecular aza-Michael reactions in tandem processes usually involves a nucleophilic nitrogen generated *in situ* by means of different organocatalyzed reactions. In this regard, a wide variety of examples can be found in the literature.[14] However, organocatalytic tandem reactions initiated by an IMAMR are scarcely reported.[15]

On the other hand, the generation of a Michael acceptor in the presence of the nitrogen nucleophile is not obvious since a spontaneous cyclization can take place in a noncatalyzed manner. In this context, the use of nitrogen sources with an attenuated nucleophilicity, such as carbamates or sulfonamides, has been crucial to overcome this issue.[16] However, the use of amides as nitrogen sources in an organocatalytic and enantioselective IMAMR is less common due to their low nucleophilicity, usually performing with moderate levels of enantioselectivity.[17]

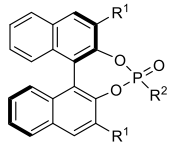
Considering this background, we decided to explore the feasibility of the unprecedented IMAMR–IMCA tandem protocol by employing compound **3a** as a model substrate. It bears an amide functionality as the nitrogen source and was prepared by means of the cross-metathesis (CM) reaction of *N*-(2,2-dimethyl-4-pentenyl)-4-oxo-2-pentenamide **1a** with methyl vinyl ketone **2a**. With conveniently functionalized amide **3a** in hand, the screening of the reaction conditions to carry out the projected tandem process began with catalyst **I** (9-amino-9-deoxy-*epi*-hydroquinine) and trifluoroacetic acid as the cocatalyst (1:1 ratio), since this catalytic system had provided excellent results in the IMAMR of conjugated ketones with either carbamates or sulfonamides as nitrogen sources.[16] However, in this case the reaction did not proceed at all, recovering the starting material unaltered (Table 1, entry 1). The next attempt was performed with thiourea **II** derived from quinine derivative **I**, leading to the desired tandem adduct **4a** in 17% yield and low enantioselectivity (Table 1, entry 2). Fortunately, the use of chiral BINOL-derived phosphoric acids dramatically changed the situation.[18] When the reaction was performed with naphthyl-derived catalyst **III**, we observed the complete conversion of the starting material, and the tandem pyrrolizidinone product **4a** was obtained in 57% isolated yield and 83% enantiomeric excess (Table 1, entry 3). Changing the

Table 1. Optimization of the Tandem IMAMR–IMCA Reaction





I : R = H
II : R =



III (R^1 = 1-naphthyl, R^2 = OH)
IV (R^1 = 9-anthryl, R^2 = OH)
V (R^1 = 2,4,6-triisopropylphenyl, R^2 = OH)
VI (R^1 = 2,4,6-triisopropylphenyl, R^2 = NH-SO_2CF_3)

entry	catalyst	solvent	**4** (% yield)[a]	ee (%)[b]
1	**I**/TFA	$CHCl_3$		
2	**II**	$CHCl_3$	17	18
3	**III**	$CHCl_3$	57	83[c]
4	**IV**	$CHCl_3$	63	89[c]
5	**V**	$CHCl_3$	59	>99[c]
6	**VI**	DCM	65	81[c]
7	**V**	toluene	67	97[c]
8	**V**	THF	34	42[c]
9	**V**	DCM	61	>99[c]

[a]Isolated yield after flash column chromatography. [b]Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details). [c]Final product **4a** was formed as a single diastereoisomer.

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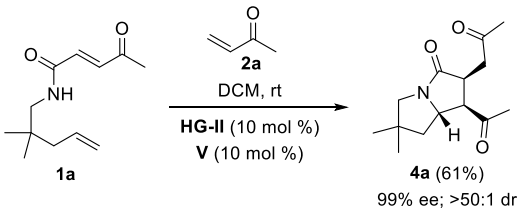
catalyst to chiral BPA **IV** translated to a small improvement in the final ee value (Table 1, entry 4); meanwhile with (*R*)-TRIP-derived BPA **V**, the tandem process took place in good yield and with outstanding enantiocontrol, giving rise to compound **4a** as a single enantiomer (Table 1, entry 5). When the more acidic triflimide **VI** was employed, a remarkable drop in the enantioselectivity was observed (Table 1, entry 6). The use of other solvents, such as toluene or THF, did not improve the tandem process (Table 1, entries 7 and 8, respectively), while dichloromethane afforded comparable results to those obtained in $CHCl_3$ (Table 1, entry 9).

In view of the above results, the treatment of amide **3a** with (*R*)-TRIP-BPA (10 mol %) in dichloromethane at room temperature for 12 h was established as the optimal conditions for the tandem IMAMR−IMCA reaction (Table 1, entry 9).

As was mentioned previously, chiral BINOL phosphoric acids are compatible with a wide variety of catalysts, including metathesis ruthenium carbenes. The synergy between the second generation Hoveyda−Grubbs catalyst (**HG-II**) and chiral BPAs in tandem protocols was previously described by several authors.[19] Hence, we envisioned the possibility of merging our organocatalytic tandem IMAMR−IMCA protocol with the initial cross-metathesis reaction to perform the whole sequence in a single operation. To our delight, when substrate **1a** was treated with the **HG-II** catalyst, chiral BPA **V**, and methyl vinyl ketone **2a** in dichloromethane at room temperature for 12 h, compound **4a**, which arose from a triple-tandem reaction, was obtained in a 61% yield with complete diastereo- and enantioselectivity (Scheme 2). This multiple-relay catalytic process was further extended to other starting *N*-pentenyl-4-oxo-2-alkenamides **1**. The results obtained are summarized in Scheme 3.

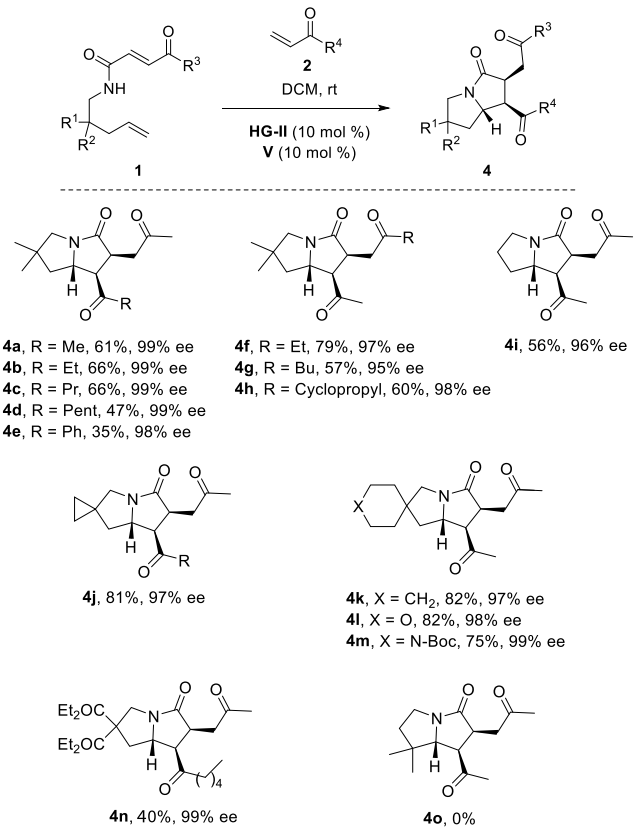
Scheme 2. CM/IMAMR−IMCA Sequence on Substrate 1a



Regarding the vinyl ketone counterpart, both aliphatic (**4a−d**) and aromatic (**4e**) conjugated ketones readily undergo the tandem CM−IMAMR−IMCA process, providing the corresponding pyrrolizidinone derivatives **4** in reasonable yields and excellent enantiocontrol. The modification of the starting alkenamides **1** at the conjugated ketone substituent was also possible, rendering final products **4f−h** in a very efficient manner. Substitution at the pyrrolidinone ring was evaluated next. Either unsubstituted pyrrolidinone **4i** or pyrrolidinones **4j−m** bearing spirocyclic moieties such as cyclopropyl, cyclohexyl, tetrahydropyranyl, or *N*-Boc-piperidinyl at position 6 were obtained very efficiently. Likewise, the inclusion of a *gem*-diester moiety was able to give compound **4n** in an efficient manner. Finally, the 7-*gem*-dimethyl derivative **4o** was not obtained, but the corresponding starting amide remained unaltered under the reaction conditions. This could be explained because of the increasing steric requirements at the double bond, thus avoiding the initial CM reaction.[20]

The absolute configuration of the three newly created stereocenters in the triple-tandem reaction was assigned by X-ray analysis. Crystals of pyrrolizidinone **4a** suitable for single-crystal X-ray diffraction were grown from an *i*-Pr_2O solution, and its structure was found unambiguously. An identical stereochemical outcome was assumed for all other pyrrolizidinones **4**.

Scheme 3. Scope of the Triple-Tandem Protocol[a,b,c]



[a]Unless otherwise noted, reactions were carried out with **1** (0.2 mmol), catalyst **V** (10 mol %), **HG-II** (10 mol %), and the corresponding conjugated ketone **2** (4 equiv) in dichloromethane (2 mL) at room temperature for 12 h. [b]In all examples, only one diastereoisomer was detected by ^{1}H NMR of the crude reaction mixtures. [c]Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).

A possible explanation to rationalize the stereochemical outcome of the process with a simple model can be proposed as follows. The chiral Brønsted acid catalyst plays a bifunctional role, activating both the nucleophile and the electrophile for the IMAMR simultaneously. Therefore, chiral phosphoric acid **V** would establish hydrogen bonds with the H of the amide nitrogen and also with the ketone carbonyl of the Michael acceptor, thus promoting the nucleophilic attack to the *si*-face of the double bond. The subsequent IMCA would again be activated by the chiral catalyst through the double hydrogen-bonding interaction with the enol nucleophile and the second conjugated ketone moiety. In this manner, the nucleophilic attack to the *re*-face of the double bond would produce the observed *cis*-substituted adduct in the second cyclization (Scheme 4).

As a further extension of this work, an intramolecular aldolic event, followed by dehydration, occurred when compound **4a** was treated with TsOH at room temperature, giving rise to tricyclic derivative **5** in 65% yield. With this result in hand, we envisioned the possibility of performing the whole sequence in

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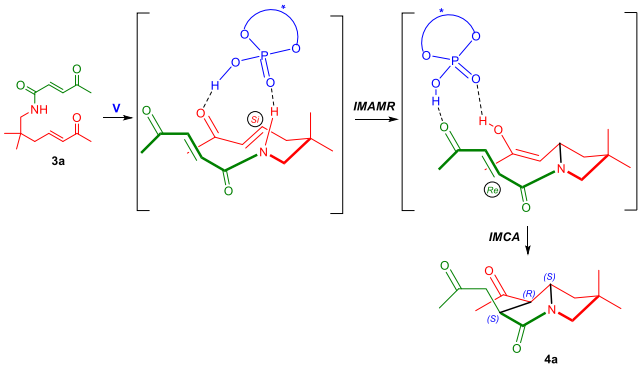
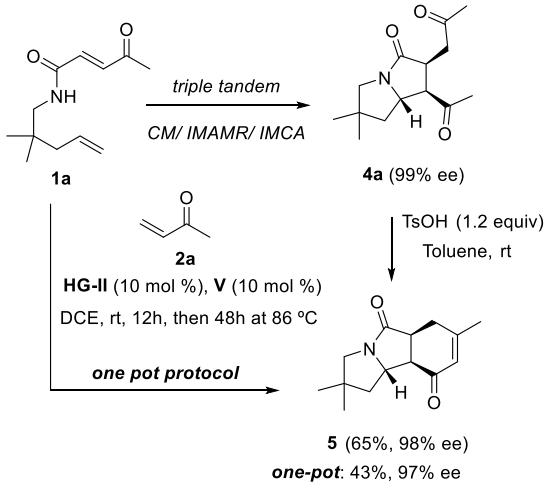
Scheme 4. Plausible Mechanistic Pathway for the IMAMR–IMCA Tandem Process



a one-pot manner taking advantage of the phosphoric acid to effect the final cyclization. Hence, a solution of compound **1a** in dichloroethane was subjected to the standard triple-tandem reaction conditions until TLC revealed the complete formation of pyrrolizidinone **4a**. Then, the reaction mixture was heated at 86 °C; after 48 h, the disappearance of compound **4a** was observed, while final tricycle derivative **5** could be isolated in a 43% overall yield (Scheme 5).

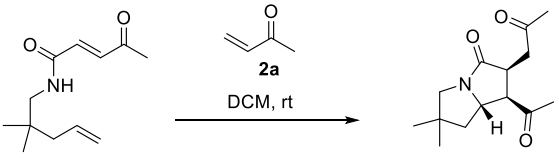
Scheme 5. CM/IMAMR/Robinson Annulation Sequence for the Synthesis of Tricyclic Derivative 5



Finally, the synthesis of pyrrolizidinone **4a** was tested on a multigram scale. As it was shown in Scheme 3, starting from 42 mg of **1a** (0.2 mmol), 29 mg of the triple-tandem product **4a** was obtained (61% yield). When the reaction was performed with 600 mg of **1a** and the catalyst loading was also reduced to 5 mol %, 500 mg of compound **4a** was obtained (69% yield) without erosion of the enantioselectivity. In addition, the tandem protocol was effected on a 1200 mg scale, in this case decreasing the catalyst loading to 2%. Again, the reaction was found to be highly efficient, giving 1011 mg of the final product **4a** as well as no erosion of the ee value (Scheme 6).

In conclusion, the enantioselective synthesis of a new family of pyrrolizidinone derivatives has been described. These scaffolds are present in a wide variety of natural products and biologically relevant compounds. The synthetic strategy involved a triple-tandem cross metathesis–intramolecular aza-Michael reaction–intramolecular Michael addition of *N*-pentenyl-4-oxo-2-alkenamides in their reaction with conjugated ketones. This multiple-relay-catalyzed process takes advantage of the synergy between the second generation Hoveyda–Grubbs catalyst and chiral (*R*)-TRIP-derived BINOL phosphoric acid. This catalytic system enables the overall transformation in a cooperative manner, rendering final products with three contiguous stereocenters in good yields, total diastereoselectivity, and excellent enantioselectivity. It is important to note that the intramolecular aza-Michael reaction takes place with amides as the nucleophilic nitrogen source. Furthermore, the triple tandem reaction was coupled with a third cyclization process (Robinson annulation) in a one-pot manner just by heating the reaction mixture.

Scheme 6. Scale-Up of the Triple-Tandem Protocol



1a	HG-II	V	4a
42 mg	10 mol %	10 mol %	29 mg (61%, 99% ee)
600 mg	5 mol %	5 mol %	500 mg (69%, 99% ee)
1200 mg	2 mol %	2 mol %	1011 mg (70%, 99% ee)

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03344.

General procedures; synthesis information of **1j**, **1k**, **3a**, and **5a**; X-ray data; HPLC traces of **4** and **5**; and NMR and HMBC spectra (PDF)

Accession Codes

CCDC 2032501 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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