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Tandem Enantioselective Cycloaromatization/Intramolecular Friedel–Crafts Desymmetrization of Cyclohexadienones

Daniel Gaviña,[a] Marta Durán,[a] Lidia Prieto,[a] Marcos Escolano,[a] Santiago Díaz-Oltra,[a] María Sánchez-Roselló,[a,*] and Carlos del Pozo[a,*]

[a] Department of Organic Chemistry, University of Valencia, E-46100 Burjassot, Spain
E-mail: carlos.pozo@uv.es; maria.sanchez-rosello@uv.es

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Abstract: An enantioselective tandem sequence that comprises a cycloaromatization process followed by an intramolecular desymmetrizing Friedel-Crafts alkylation of functionalized cyclohexadienones has been accomplished. The process takes place in good yields (65–95%), with excellent diastereoselectivity (>20:1) and enantiomeric ratios up to 90.5:9.5 in the presence of (*R*)-BINOL-derived *N*-triflyl phosphoramides, and it gains access to a family of pyrrolo[2,1-*a*]isoquinoline derivatives in a simple manner, with the simultaneous generation of two vicinal stereocenters, one of them a tetrasubstituted carbon stereocenter.

Keywords: Cycloaromatization; Intramolecular friedel-crafts alkylation; Cyclohexadienones; Desymmetrization; Tandem reactions

Introduction

Tandem reactions, meaning processes where several bond-forming reactions take place under the same conditions, without needing to add further reagents or catalysts, are particularly convenient from a Green Chemistry perspective. They constitute an atom-economical and modular approach for the synthesis of complex molecules in a simple manner from readily available starting materials.[1]

On the other hand, desymmetrization reactions of achiral or meso compounds promoted by chiral catalysts have become one of the most powerful and elegant strategies for the generation of enantiomerically enriched compounds, with the simultaneous generation of multiple stereocenters.[2] Therefore, the advantages of combining tandem reactions with desymmetrization processes are obvious, as they allow the assembly of stereochemically diverse scaffolds, increasing their three dimensional content. This feature has been associated with increased success rates in clinical trials for a particular drug candidate.[3]

One of the keys of designing tandem processes is the availability of substrates bearing multiple and orthogonal reactive points, that will successively react to generate structural and stereochemical complexity. Substituted 2,5-cyclohexadienones are ideal substrates in this regard. These are versatile synthetic intermediates and appealing molecules for enantioselective desymmetrization protocols, as they possess a C2 element of symmetry. Numerous functional groups, including alkenes, alkynes, allenes, dienes, aldehydes, esters, bis-sulfones, enals and enones, have been anchored to the cyclohexadienone framework as functional handles which can undergo different intramolecular transformations. In this context, conveniently functionalized prochiral cyclohexadienones have participated in desymmetrization processes by means of conjugate additions, Rauhut-Currier reactions, Stetter- and Friedel-Crafts-type reactions, among others, to efficiently afford bicyclic and tricyclic molecules, with the generation of one or more stereocenters.[4]

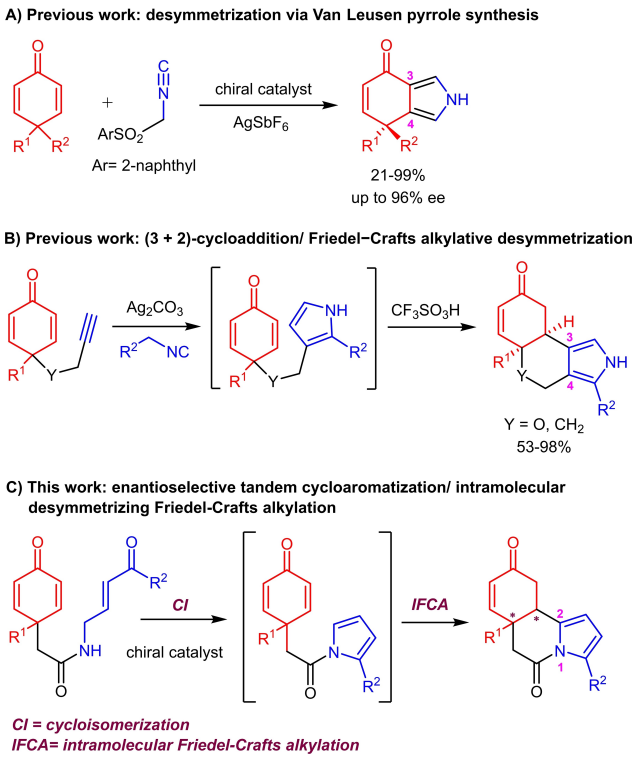
Moreover, the pyrrole moiety embedded into polycyclic scaffolds is a highly represented structural

motif in clinically useful pharmaceuticals and natural products.[5] For this reason, the development of new synthetic methodologies that gain entry to these frameworks is highly desirable.[6]

The intramolecular Friedel-Crafts alkylation (IFCA) reaction is one of the most direct ways to synthesize polycyclic pyrroles.[6a] The main limitation of this approach, in its enantioselective version, is the high reactivity of the pyrrole moiety that can trigger background processes spontaneously. Several strategies have been devised in order to overcome this problem; for example, the *in situ* generation of the electrophilic partner in the presence of the pyrrole ring by means of a cross metathesis reaction in a tandem sequence.[7] Alternatively, it is also possible to create the pyrrole moiety *in situ* from adequately functionalized substrates, that will undergo the IFCA once the ring is formed. In this context, we took advantage of this approach for the asymmetric synthesis of bicyclic and tetracyclic pyrroles, employing a cycloaromatization process, to generate the pyrrole ring, followed by an IFCA reaction,[8] and a Pictet-Spengler-type reaction,[9] respectively.

As far as we know, only two examples that merge pyrroles and cyclohexadienones for the synthesis of polycyclic pyrroles have been reported to date. The first one is an intermolecular desymmetrization process by means of the Van Leusen pyrrole synthesis, involving the reaction of cyclohexadienones with the isocyanomethyl sulfone surrogate NasMIC, under the catalysis of a chiral silver salt (Scheme 1, **A**).[10] The second one comprises a one-pot intermolecular (3 + 2) cycloaddition between cyclohexadienone-tethered alkynes and ethyl isocyanoacetates followed by a Friedel-Crafts alkylative desymmetrization process (Scheme 1, B).[11] Both examples led to pyrrole derivatives fused by the 3- and 4-positions of the ring.

In the present work, the tandem combination of a cycloaromatization process with a desymmetrizing IFCA reaction of cyclohexadienones is described. Thus, after the Brønsted acid-catalyzed pyrrole formation through cycloaromatization of *N*-4-oxo-2-alkenyl acetamides anchored to the 4-position of 2,5-cyclohexadienones, the IFCA takes place under the reaction conditions, rendering a new family of pyrrolo[2,1-*a*]isoquinoline derivatives (Scheme 1, C). In our case, the fusion of the pyrrole ring occurs at the 1- and 2-positions, which is complementary to the previously reported work. Moreover, the tandem protocol results in the simultaneous generation of two vicinal stereocenters, being one of them a tetrasubstituted carbon stereocenter. The enantioselective creation of these types of stereocenters still remains a challenge in synthetic organic chemistry,[12] as they are common structural features of a wide variety of drug molecules and natural products.



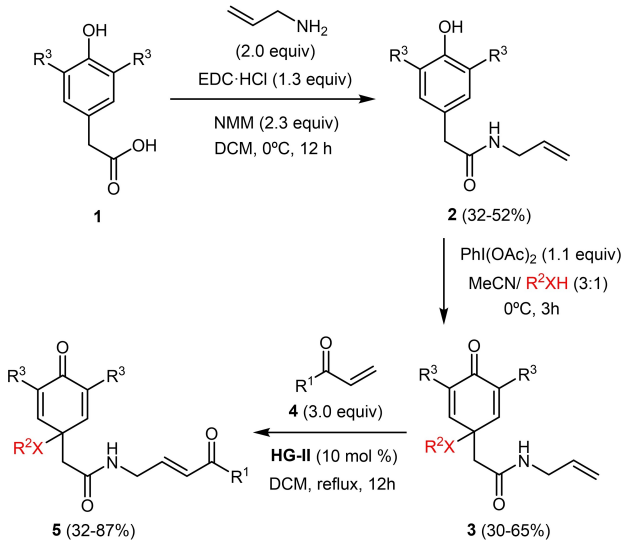
Scheme 1. Synthetic strategies towards polycyclic pyrroles involving the desymmetrization of cyclohexadienones.

Furthermore, the presence of an enone functionality in the final products provides an additional reactive site, that should allow for late-stage transformations to enrich the library with increased structural diversity.

Results and Discussion

The functionalized 2,5-cyclohexadienones required to test our protocol were readily available by oxidative dearomatization of the corresponding phenols. Accordingly, 4-hydroxyphenyl acetic acids **1** were converted into allyl amides **2** through reaction with allyl amine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as a coupling reagent and *N*-methylmorpholine (NMM). Then, the dearomatization was performed employing diacetoxyiodobenzene and different nucleophiles such as water, alcohols, acetic acid and acetamide. In this manner, 4,4-disubstituted cyclohexadienones **3** were obtained in moderate to good yields. Finally, they were coupled with conjugated ketones **4** by means of a cross metathesis (CM) reaction with 2nd generation Hoveyda-Grubbs catalyst (**HG-II**), that gave rise to compounds **5** (Scheme 2), again in moderated to good yields (See Experimental Section for details).

With starting cyclohexadienones **5** in hand, the feasibility of the tandem cycloaromatization/ Friedel-Crafts alkylation reaction was evaluated under



Scheme 2. Synthesis of cyclohexadienone-tethered *N*-4-oxo-2-alkenyl acetamides **5**.

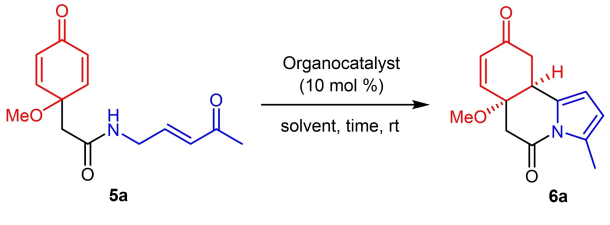
Brønsted acid catalysis. To this end, compound **5 a** was employed as a model substrate. The results of this study are summarized in Table 1.

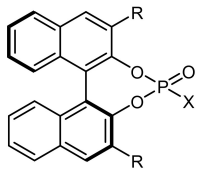
Initially, we evaluated the influence of the catalyst. Previous results from our laboratory indicated that chiral BINOL-derived phosphoric acids (BPAs) were suitable catalysts for the cycloaromatization step.[8] Therefore, compound **5 a** was treated with some BPAs (**I–V**) bearing different substitution at the 3 and 3' positions. In all cases, the desired tandem cycloaromatization/ IFCA took place in dichloromethane at room temperature with moderate to good yields, complete diastereoselectivity but very low enantioselectivity (Table 1, entries 1–5).

Given that acidity usually plays an important role in reactions catalyzed by BPAs, the corresponding *N*-triflyl phosphoramides were also screened. In general, chemical yield increased when organocatalysts **VI–X** were employed in the tandem process (Table 1, entries 6–10) and the best enantiocontrol was achieved with the phosphoramide **VI** bearing 2,4,6-triisopropylphenyl groups (85% yield and 70:30 er; Table 1, entry 6).

The influence of the solvent was examined next. Thus, the reaction in toluene took place with better enantioselectivity (78:22 er) than that observed in dichloromethane (Table 1, entry 11), while the use of xylenes and carbon tetrachloride gave rise to comparable results (Table 1, entries 12, 13). Oxygenated solvents were found to be quite suitable in terms of yield and enantioselectivity. Whereas diethyl ether and THF afforded comparable er values to that obtained in toluene (Table 1, entries 14, 15), the reaction in 1,4-dioxane led to product **6 a** in 92% yield with 86:14 er, afer 3 days at room temperature (Table 1, entry 16).

Table 1. Optimization of the enantioselective tandem reaction of substrate **5 a**.





Organocatalyst

I (R = 2,4,6-*i*-$Pr_3C_6H_2$, X = OH)
II (R = 9-anthracenyl, X = OH)
III (R = 9-phenanthryl, X = OH)
IV (R = 1-naphthyl, X = OH)
V (R = 2-naphthyl, X = OH)
VI (R = 2,4,6-*i*-$Pr_3C_6H_2$, X = NH-Tf)
VII (R = 9-anthracenyl, X = NH-Tf)
VIII (R = 9-phenanthryl, X = NH-Tf)
IX (R = 1-naphthyl, X = NH-Tf)
X (R = 2-naphthyl, X = NH-Tf)

Entry	Catalyst	t (h)	Solvent	Yield 6 a (%)[a]	er[b]
1	**I**	72	CH_2Cl_2	49	56:44
2	**II**	72	CH_2Cl_2	77	63:37
3	**III**	72	CH_2Cl_2	68	55:45
4	**IV**	72	CH_2Cl_2	72	56:44
5	**V**	72	CH_2Cl_2	71	59:41
6	**VI**	72	CH_2Cl_2	85	70:30
7	**VII**	72	CH_2Cl_2	67	57:43
8	**VIII**	72	CH_2Cl_2	67	58:42
9	**IX**	72	CH_2Cl_2	77	54:46
10	**X**	72	CH_2Cl_2	99	55:45
11	**VI**	72	Toluene	79	78:22
12	**VI**	72	CCl_4	75	79:21
13	**VI**	72	xylenes	78	76:24
14	**VI**	72	Et_2O	84	79:21
15	**VI**	72	THF	99	81:19
16	**VI**	72	dioxane	92	86:14
17	**VI**	16	dioxane	91	87:13
18	**VI**	8	dioxane	79	82:18
19	**VI**	16	Solvents[c]	70	79:21
20	**VI**[d]	16	dioxane	90	86:14

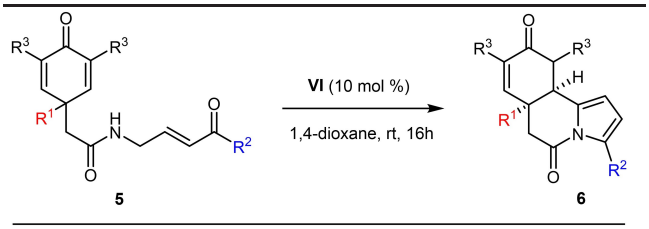
[a] Isolated yield after flash column chromatography.
[b] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).
[c] Reaction performed in THF/dioxane 1/3 at 0 °C.
[d] Catalyst loading was 20%.

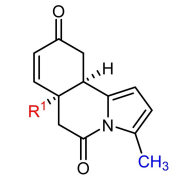
Then, the reaction time was also evaluated, and we found that the desired tandem product **6a** was isolated in 99% yield after 16 hours, with good 87:13 enantiomeric ratio (Table 1, entry 17). Shorter reaction time (8 h) did not improve the tandem process but decreased both, the chemical yield and the enantioselectivity (Table 1, entry 18). In order to test the influence of the temperature in the process, the reaction was performed in a THF/dioxane 1/3 mixture at 0 °C with decreased enantiomeric ratio (Table 1, entry 19). Finally, the

increase of the catalyst loading provided comparable results (Table 1, entry 20).

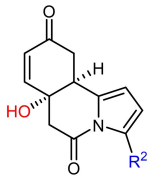
In light of these results, the optimized conditions for our tandem protocol involved the use of organocatalyst **VI** in 1,4-dioxane as the solvent, at room temperature for 16 hours. These reaction conditions were further extended to other starting cyclohexadienones **5**. Table 2 summarizes the results obtained in the evaluation of the scope and limitations of the process leading to chiral tricyclic pyrrole derivatives.

Table 2. Scope of the enantioselective cycloaromatization/desymmetrizing IFCA of cyclohexadienone derivatives **5**.[a], [b]

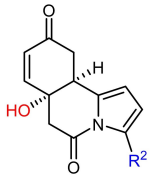




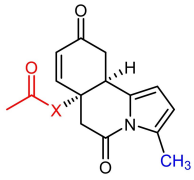
6a (R^1 = OMe, 91%, 86.5:13.5 er)
6b (R^1 = OH, 82%, 90.5:9.5 er)
6c (R^1 = OBu, 91%, 85.5:14.5 er)
6d (R^1 = O-*i*-Pr, 82%, 82.5:17.5 er)
6e (R^1 = OBn, 81%, 87:13 er)



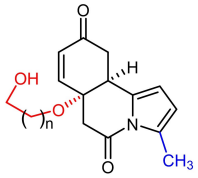
6f (R^2 = Et, 87%, 85.5:14.5 er)
6g (R^2 = Pr, 78%, 84.5:15.5 er)
6h (R^2 = *i*-Pr, 73%, 83.5:16.5 er)
6i (R^2 = Pent, 95%, 79.5:20.5 er)



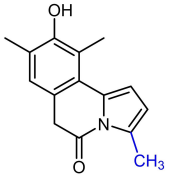
6j (R^2 = Ph, 95%, 85:15 er)
6k (R^2 = 4-MeO-C_6H_4, 65%, 87.5:12.5 er)
6l (R^2 = 4-Cl-C_6H_4, 73%, 85:15 er)



6m (X = O, 65%, 89:11 er)
6n (X = NH, 76%, 80.5:19.5 er)



6o (n = 1, complex mixture)
6p (n = 2, 80%, 86:14 er)



7 (36%) [c]

[a] Reactions were carried out in a 0.1 mmol scale with **5** (1 equiv.) and **VI** (0.1 equiv.) in 1,4-dioxane (0.05 M).
[b] In all cases, products **6** were obtained as single diastereoisomers. Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).
[c] This reaction was performed in refluxing 1,4-dioxane for 16 h.

The substitution at the tetrasubstituted carbon stereocenter (R^1) was studied first. Accordingly, water and several alcohols had been introduced at the oxidation stage and the corresponding functionalized cyclohexadienones **5a–e** were subjected to the optimized conditions mentioned above to afford tricyclic pyrroles **6a–e** in excellent yields (81–91%), with complete diastereoselectivity and moderate to good enantioselectivity. The best enantiomeric ratio (90.5:9.5 er) was obtained for compound **6b** containing a hydroxyl group at the tetrasubstituted carbon stereocenter, which indicates that the enantioselectivity of the tandem process seems sensitive to steric effects.

The conjugated ketone moiety was the next position to be evaluated. In this context, final products **6f–i** bearing aliphatic substituents at the pyrrole ring (R^2) were formed in good yields (73–95%), with moderate to good er values. Again, increasing steric requirements at this position negatively affected the enantioselectivity. Aromatic enones **5j–l** were also tolerated in the tandem process, leading to the corresponding pyrrole derivatives **6j–l** in good yields (65–95%) and moderate to good enantioselectivities, regardless the presence of electron donating or electron withdrawing groups in the aromatic ring.

Other nucleophiles different from alcohols had been incorporated at the tetrasubstituted carbon stereocenter and they were also compatible with the tandem protocol, giving rise to products **6m**, **n** bearing an *O*-acetyl and acetamide groups, respectively. On the other hand, substrate **5o**, containing an ethylene glycol moiety, provided a complex mixture of products, probably due to the competing intramolecular oxa-Michael reaction that could take place under the reaction conditions. This oxa-Michel event was avoided with substrate **5p** bearing a propylene glycol moiety at the tetrasubstituted carbon stereocenter. In this case, the formation of a 7-membered ring would not be favoured and the oxa-Michael reaction did not compete with the cycloisomerization protocol, giving rise to the desired tricyclic pyrrole **6p** in 80% yield and 86:14 er.

Finally, substrate **5q** containing two methyl groups at the 2 and 6 positions of the cyclohexadienone moiety (R^3 position) was subjected to the reaction conditions; however, only the cycloaromatization process took place in this case. When the reaction was performed in refluxing dioxane, the IFCA reaction occurred, albeit with a concomitant dehydration event to yield the tricyclic phenol derivative **7** in 36% yield (Table 2).

The absolute configuration of the newly created stereocenters in the tandem protocol was assigned by X-ray analysis. Crystals of tricyclic pyrrole **6b** suitable for single-crystal X-ray diffraction displayed the

absolute configuration showed in Table 2.[13] An identical stereochemical outcome was assumed for all other compounds **6**.

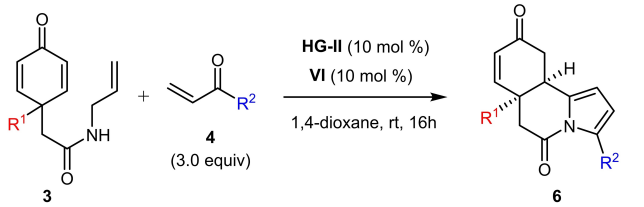
The compatibility of chiral BINOL phosphoric acids with different catalysts has been exploited in a wide variety of transformations in order to develop tandem or one-pot processes. Specifically, the synergy between BPAs and second generation Hoveyda-Grubbs catalyst has been reported by several authors.[7,14] In this context, we wonder if BINOL-derived *N*-triflyl phosphoramides would be also compatible with Hoveyda-Grubbs catalysts, aiming at incorporating the initial CM reaction to our tandem cycloaromatization/IFCA to perform the whole sequence in a single operation. To our delight, when cyclohexadienone derivative **3a** and methyl vinyl ketone **4a** were treated with **HG-II** and chiral BPA phosphoramide **VI** in 1,4-dioxane at room temperature for 16 h, the tricyclic pyrrole product **6a** was obtained in 69% yield and 86.5:13.5 er (Table 3, entry 1). Comparison with the stepwise protocol showed that this tandem variant took place with improved yield while maintaining the enantiocontrol.

The triple tandem protocol was also evaluated with substrate **3b** (R^1 = OH) and aliphatic enones, providing in all cases the corresponding tricyclic pyrrole derivatives **6b**, **f**, **g**, **i** with comparable er values and slightly better yields than those obtained in the stepwise process (Table 3, entries 2–5). However, the reaction with phenyl vinyl ketone did not work, probably because the cross-metathesis reaction of substrate **3b** with this aromatic enone is very slow and, after 16 hours, we did not detect product **6j** in the reaction mixture (Table 3, entry 6). It is important to point out that, as far as we know, this is the first example that combines a chiral BPA-derived triflimide with a ruthenium carbene.

The whole synthesis of product **6b** was tested on a multigram scale. Thus, starting from 1.24 g of cyclohexadienone-derived amide **3b** (5 mmol), 752 mg of tricyclic pyrrole **6b** were obtained; *i.e.*, this compound was formed in 65% overall yield and 90.5:9.5 er, without erosion of the yield nor the enantioselectivity of the process.

Finally, the presence of a cyclohexenone moiety in the compounds **6** allowed for late-stage transformations that would enrich the skeletal diversity of the final products. This is the case of compound **6p**, suitable to undergo an intramolecular oxa-Michael reaction. Consequently, treatment of **6p** with *p*-toluenesulfonic acid, in dichloromethane at room temperature, led to the formation of the tetracyclic pyrrole derivative **8**, after 24 hours, in 47% yield with complete diastereoselectivity (Scheme 3).

Table 3. Triple tandem CM/ cycloaromatization/ desymmetrizing IFCA of cyclohexadienone derivatives **3**.[a]



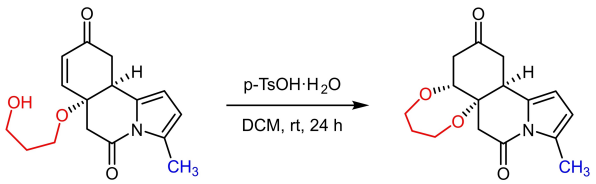
Entry	3	R^1	R^2	6, yield %[b]	er[d]
1	**3a**	OMe	Me	**6a**, 69 (60)[c]	86.5:13.5
2	**3b**	OH	Me	**6b**, 66 (50)[c]	90.5:9.5
3	**3b**	OH	Et	**6f**, 41 (36)[c]	85.5:14.5
4	**3b**	OH	Pr	**6g**, 39 (33)[c]	84.5:15.5
5	**3b**	OH	Pent	**6i**, 42 (41)[c]	80:20
6	**3b**	OH	Ph	**6j**, 0 (21)[c]	–

[a] Reactions were carried out in a 0.1 mmol scale with **3** (1 equiv.), conjugated ketone **4** (3 equiv.), **HG-II** (0.1 equiv.) and **VI** (0.1 equiv.) in 1,4-dioxane (0.05 M).
[b] Isolated yields after flash column chromatography.
[c] In brackets, combined yields of the CM reaction and the tandem cyclization in a stepwise manner.
[d] In all cases, products **6** were obtained as single diastereoisomers. Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).

Conclusion

In summary, we have developed a tandem organocatalyzed cycloaromatization/ intramolecular Friedel-Crafts desymmetrization sequence of 2,5-cyclohexadienones tethered with a *N*-4-oxo-2-alkenyl acetamide unit. The tandem enantioselective reaction took place with (*R*)-BINOL-derived TRIP-*N*-triflyl phosphoramide as a Brønsted acid catalyst, rendering tricyclic pyrrole derivatives in good overall yields (65–95%), with complete diastereoselectivity and moderate to good enantiomeric ratios (ranging from 79.5:20.5 to 90.5:9.5) in the simultaneous generation of two stereocenters, one of them a tetrasubstituted carbon stereocenter.

Moreover, the initial cross-metathesis reaction, required to assemble the starting substrates, was incorporated to the tandem protocol. Thus, the triple



6p (86:14 er) **8** (47%, 86.5:13.5 er)

Scheme 3. Intramolecular oxa-Michael reaction of compound **6p**.

tandem CM/ cycloaromatization/ IFCA occurred by combining a chiral BPA-derived triflimide with second generation Hoveyda-Grubbs catalyst.

Experimental Section

General Procedure for the Tandem Enantioselective Cycloaromatization/IFCA Cascade Sequence for the Synthesis of Compounds 6

To a solution of 5 (0.1 mmol, 1 equiv.) in 1,4-dioxane (1 mL, 0.1 M), triflimide VI (8.8 mg, 0.1 equiv.) was added. The resulting mixture was stirred at room temperature during 16 h. Then, the crude was concentrated to dryness and purified by flash column chromatography on silica gel using mixtures of *n*-hexane and ethyl acetate as eluents.

(6a*R*,10a*S*)-6 a-Methoxy-3-methyl-6,6 a,10,10 a-tetrahydropyrrolo[2,1-a]isoquinoline-5,9-dione (6 a)

Starting from 5a and following the general procedure described before, 6a (22 mg, 91%, 86.5:13.5 er) was obtained as a white solid after purification by column chromatography with Hex: EtOAc (3:1) as eluent. The er value was determined by HPLC analysis using a Phenomenex Cellulose 4 column (hexane: isopropanol 80:20); flow rate = 1.0 mL/min, t_{major} = 44.9 min, t_{minor} = 31.8 min. M.p. = 55–57 °C. $[\alpha]^{25}_{D}$ = -96 (c 1.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 10.3 Hz, 1H), 6.15 (dd, *J* = 10.3, 0.7 Hz, 1H), 5.95 (dd, *J* = 3.2, 1.0 Hz, 1H), 5.91 (dq, *J* = 3.2, 1.1 Hz, 1H), 3.81 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.28 (s, 3H), 3.04 (d, *J* = 16.7 Hz, 1H), 2.93 (dd, *J* = 16.7, 1.1 Hz, 1H), 2.90 (ddd, *J* = 17.1, 4.8, 0.7 Hz, 1H), 2.67 (dd, *J* = 17.1, 10.8 Hz, 1H), 2.48 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.4, 166.2, 149.8, 132.7, 131.8, 131.2, 112.4, 109.56, 75.3, 51.4, 42.3, 41.8, 36.3, 15.9. HRMS (ESI/Q-TOF) calculated *m/z* $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found 246.1116.

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