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Letter

Asymmetric Synthesis of [2.2.2]-Bicyclic Lactones via All-Carbon Inverse-Electron-Demand Diels–Alder Reaction

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Cite This: *Org. Lett.* 2020, 22, 1813–1817

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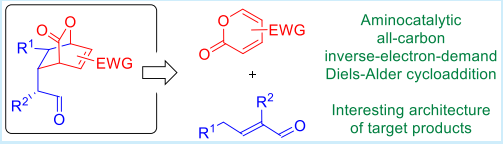
ABSTRACT: In this paper, a new cycloaddition between α,β-unsaturated aldehydes and coumalates realized under dienamine activation has been described. The reaction proceeds regioselectively with the distal double bond of the dienamine system acting as electron-rich dienophile. It leads to the formation of biologically relevant [2.2.2]-bicyclic lactones. Their functionalization potential has been confirmed in selected, diastereoselective transformations.



The chemistry of bicyclic compounds constitutes an important and developing field of research with various natural products and biologically relevant molecules containing that specific molecular motif.[1] High structural rigidity and well-defined spatial arrangements of substituents stand behind a great success of this class of compounds. Among them, bicyclic systems containing a heterocyclic δ-lactone ring occupy a prominent position (Figure 1, top).[2] Such a structural motif

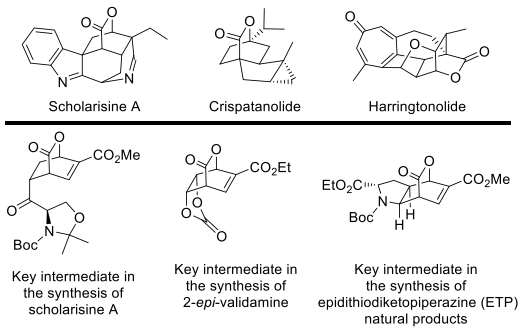
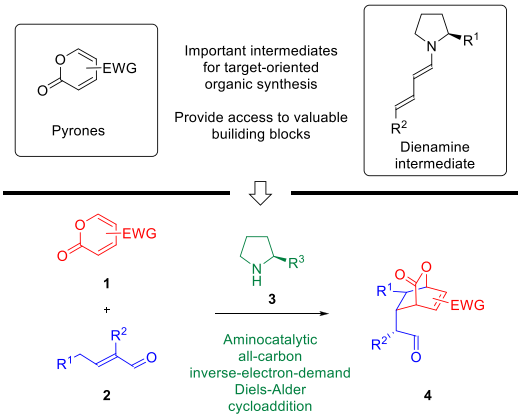


Figure 1. Importance of [2.2.2]-bicyclic lactones

can be found in scholarisine A[2a] (compound isolated from *Alstonia scholaris*) and crispatanolide[2b,c] (natural product isolated in 1980 from *Makinoa crispata* (liverwort)) as well as in the products from the harringtonolide family.[2e−g] Furthermore, the ability of bicyclic systems possessing a δ-lactone ring incorporated to undergo decarboxylative transformations to provide access to important building blocks capable of further derivatizations has found important applications in target oriented synthesis.[3,4] Selected important building blocks of such a type are shown in the bottom of Figure 1.

Pyrones including coumalate derivatives constitute useful building blocks commonly utilized in the synthesis of [2.2.2]-bicyclic lactones (Scheme 1, top).[3a,c,5] Their ability to act as dienes in the all-carbon inverse-electron-demand Diels–Alder

Scheme 1. Importance of Coumalates and Dienamine Activation and the Synthetic Objectives of Our Study



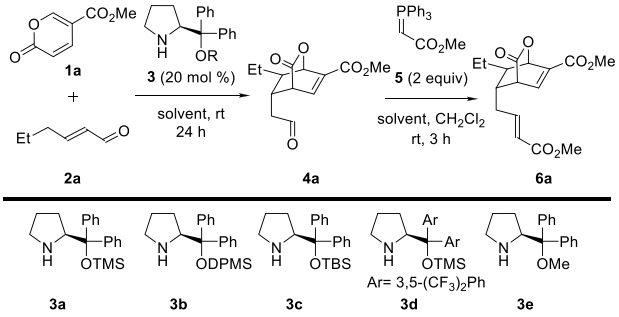
(IEDDA) cycloaddition[6] is well recognized and utilized in selected target-oriented syntheses. The functionalization potential of such cycloadducts is connected with the presence of the double bond in their structure and the possibility to perform a subsequent decarboxylative retro-Diels–Alder reaction.

Dienamine activation constitutes a powerful means for the introduction of chirality into target molecules (Scheme 1, top).[7,8] The ability of dienamine intermediates to participate in various types of cycloadditions is well recognized making such a catalytic reactions a reliable tools in the synthesis of complex molecular scaffolds.[8] Given the usefulness of [2.2.2]-bicyclic lactones, it was envisioned that the reaction between dienamines, generated catalytically in situ from α,β-unsaturated

Received: January 10, 2020
Published: February 17, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00138
Org. Lett. 2020, 22, 1813–1817

Table 1. Asymmetric Synthesis of [2.2.2]-Bicyclic Lactones 6: Optimization Studies[a]



entry	solvent (catalyst)	additive	conv. [%][b]	dr[c]	er[d]
1	CH_2Cl_2 (**3a**)		67	10:1:0:0	70:30
2	CH_2Cl_2 (**3b**)		52	13:2:1:1	n.d.
3	CH_2Cl_2 (**3c**)		73	27:1.5:1:0	80:20
4	CH_2Cl_2 (**3d**)		12	n.d.	n.d.
5	CH_2Cl_2 (**3e**)		23	n.d.	n.d.
6	$CHCl_3$ (**3c**)		>95	14:1.5:1:0	77:23
7	$ClCH_2CH_2Cl$ (**3c**)		60	44.5:2:4:1	83:17
8	toluene (**3c**)		71	12:1:5:2	n.d.
9	CH_3CN (**3c**)		47	22:2:1:0	n.d.
10	1,4-dioxane (**3c**)		43	14:3:1:1	n.d.
12	THF (**3c**)		46	14:2.5:1:1	n.d.
13	Et_2O (**3c**)		95(92)	20:1.5:3:1	96:4
14	Et_2O (**3c**)	NaOAc	83	15:5:1:1	91:9
15	Et_2O (**3c**)	$PhCO_2H$	81	11:1:2:2	89:11
16	Et_2O (**3c**)	DMABA	90	15:3:1:1	91:9
17[e]	Et_2O (**3c**)		57	17:3.5:1.5:1	n.d.

[a]All reactions were performed in a 0.1 mmol scale using **1a** (1.5 equiv) and **2a** (1.0 equiv) in 0.4 mL of corresponding solvent. [b]Determined by ^{1}H NMR of crude reaction mixture. In parentheses, the isolated overall yield for **6a** is given. [c]Determined by ^{1}H NMR of crude reaction mixture after the first step. [d]Determined by chiral HPLC for **6a**. [e]The reaction was performed at 0 °C for 48 h. DMABA: 4-(dimethylamino)benzoic acid.

aldehydes and secondary amines, and selected pyrones might constitute a useful and powerful approach to such systems. Notably, the applications of methyl coumalate and related systems in the all-carbon IEDDA reactions with electron-rich double bonds is quite limited and enantioselective variants of such reactions are very limited.[5k,9]

Herein, we present our studies on the all-carbon IEDDA cycloaddition between α,β-unsaturated aldehydes and selected pyrones proceeding according to dienamine activation (Scheme 1, bottom). The usefulness of the cycloadducts obtained has been confirmed in selected, stereoselective transformations leading to higher molecular and stereochemical complexity.

At the outset of our studies, simple and readily available *trans*-2-hexenal **2a** and methyl coumalate **1a** were selected as model substrates for the envisioned organocatalytic inverse-electron-demand all-carbon Diels–Alder cycloaddition realized according to dienamine activation. Initially, the reaction was performed in dichloromethane using diphenylprolinol trimethylsilyl ether **3a** as the aminocatalyst. To our delight, the reaction proceeded smoothly affording **4a** with good diastereoselectivity (Table 1, entry 1). However, we were unable to isolate it as **4a** proved to be unstable under flash chromatography conditions. Therefore, the derivatization of **4a** via Wittig reaction performed in a *one-pot* fashion was attempted. Compound **6a** was formed within 3 h and isolated by flash chromatography. Its chiral stationary phase HPLC analysis indicated that the initial organocatalytic reaction proceeded with poor enantioselectivity. Therefore, the search for optimal aminocatalyst **3** ensuring high efficiency and stereoselectivity of the process was initiated. It was found that, among catalysts tested, the use of amine **3c** bearing the bulkier *tert*-butyldimethylsilyl group at the oxygen atom promoted the reaction with increased conversion, providing the product **6a** with improved diastereo- and enantioselectivity (Table 1, entry 3). Subsequently, the solvent screening was performed. It was found that the use of other chlorinated solvents such as chloroform and 1,2-dichloroethane did not significantly influence the reaction (Table 1, entries 6, 7). Similarly, toluene and most of the polar aprotic solvents such as acetonitrile, 1,4-dioxane, and tetrahydrofuran did not provide the significant improvement of the results (Table 1, entries 8–12). Interestingly, the reaction in diethyl ether proceeded efficiently and in a highly diastereo- and enantioselective manner (Table 1, entry 13). In the course of further studies, the influence of various additives was tested. However, neither acidic nor basic cocatalysts enhanced the reaction stereoselectivity and efficiency (Table 1, entries 14–16). Finally, the influence of temperature was evaluated (Table 1, entry 17). Unfortunately, the decrease of the temperature to 0 °C led to lower conversion and to a decrease of diasteoselectivity, thus indicating the final reaction parameters (Table 1, entry 13).

With the optimized reaction conditions in hand, the substrate scope of the all-carbon asymmetric IEDDA reaction was explored (Table 2). To our delight, the reactions with a series of linear α,β-unsaturated aldehydes **2a–e** with different chain lengths proceeded smoothly affording, after the Wittig reaction, the corresponding products **6a–e** in high yields and

https://dx.doi.org/10.1021/acs.orglett.0c00138
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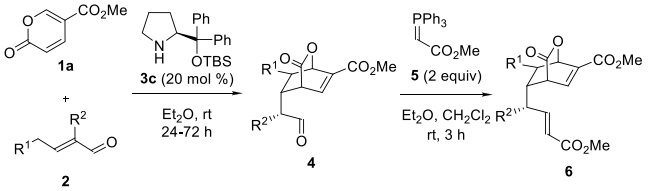
Table 2. Asymmetric Synthesis of [2.2.2]-Bicyclic Lactones 6: Enal 2 Scope[a]



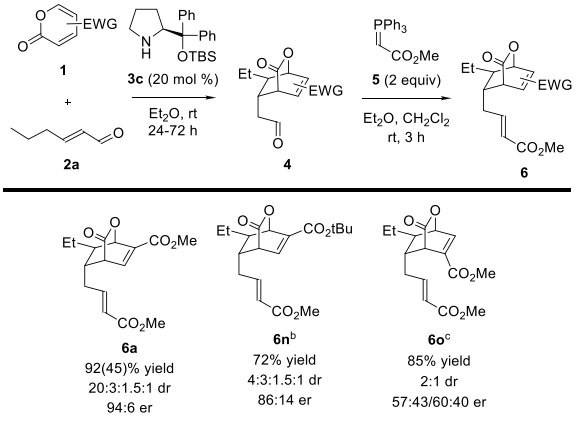
entry	R^1	R^2	yield [%][b]	dr[c]	er[d]
1	Et	H	92(45)	20:3:1.5:1	94:6
2	Me	H	76	9:4:1:1	92.5:7.5
3	*n*Pr	H	80(52)	28:6:2:1	94.5:5.5
4	*n*Bu	H	90	26:4:2:1	93.5:6.5
5	*n*Pn	H	83	32:5:2:1	94:6
6	Bn	H	85(62)	13:1.1:1	92:8
7	*E*-2-Pn	H	86	43:5:2.5:1	91.5:8.5
8	*Z*-2-Pn	H	82	79:5:4:1	94:6
9[e]	Ph	H	62	34:2:2:1	95:5
10[f]	4-FC_6H_4	H	54	21:3:1:0	94:6
11[f]	4-$CF_3C_6H_4$	H	45	26:2:1.5:1	99:1
12[e]	3,4-$(MeO)_2C_6H_3$	H	65	13:1.5:1.5:1	98:2
13	*i*Pr	Ph	83	4:1:0:0	99.5:0.5
14[g]	Et	H	87(57)	15.5:1.5:2:1	94:6

[a]All reactions were performed in a 0.1 mmol scale using **1a** (1.5 equiv) and **2** (1.0 equiv) in 0.4 mL of diethyl ether (for details, see the Supporting Information). [b]Isolated yields over two steps are given. In parentheses, isolated yields of major diastereoisomer of **6** in a diastereomerically pure form are given. [c]Determined by ^{1}H NMR of crude reaction mixture after the first step. [d]Determined by chiral HPLC analysis for **6**. [e]Reaction performed using **1a** (1.0 equiv) and **2** (2.2 equiv) for 72 h. [f]Reaction performed using **1a** (1.0 equiv) and **2** (2.2 equiv) for 96 h. [g]Reaction performed on a 1 mmol scale.

enantioselectivities and good diastereoselectivities (Table 2, entries 1−5). It is worth noting that the length of the alkyl side chain had an influence on the reaction diastereoselectivity. The use of *trans*-2-pentenal **2b** (Table 2, entry 2) provided the product **6b** with worse diastereomeric ratio than in the case of enals **6c−e** with longer alkyl chains (Table 2, entries 3−5). Furthermore, the introduction of functional groups in the side-chain of the alkyl group in **6** proved possible. The introduction of phenyl group or a double bond (either *E*- or *Z*-configured) did not affect the outcome of the cycloaddition yielding [2.2.2]-bicyclic lactones **6f−h** with high yield and reasonable diastereo- and enantiomeric excesses (Table 2, entries 6−8). Subsequently, the possibility to introduce various aromatic group in the C7 position of the final product **6** was attempted (Table 2, entries 9−12). To our satisfaction, the expected products **6i−l** bearing phenyl rings with various electronic properties and substitution patterns were obtained with good results. However, the use of slightly modified conditions involving larger aldehyde excess (2.2 equiv) and prolonged reaction time (72−96 h) was required. The developed method proved also unbiased toward α-substituted enals **2m** as demonstrated in the synthesis of **6m** (Table 2, entry 13). The desired product **6m** bearing an additional stereogenic center was obtained in very good yield and excellent enantiomeric excess. Notably, **6m** was obtained as a mixture of only two diastereoisomers. Reaction proved also readily scalable to 1 mmol scale as demonstrated in the synthesis of **6a** (Table 2, entry 14).

Further scope studies were focused on the utilization of various pyrone derivatives **1b,c** in the reaction (Scheme 2). It

Scheme 2. Asymmetric Synthesis of [2.2.2]-Bicyclic Lactones 6: Pyrone 1 Scope[a]

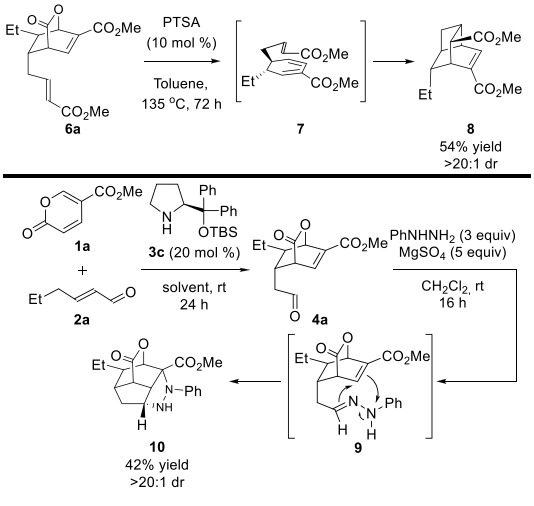


[a]All reactions were performed in a 0.1 mmol scale using **1a** (1.5 equiv) and **2** (1.0 equiv) in 0.4 mL of diethyl ether (for details, see the Supporting Information). Isolated yields are given. In parentheses, isolated yields of the major diastereoisomer are given; dr was determined by ^{1}H NMR of the crude reaction mixture; er was determined by chiral HPLC analysis for **6**. [b]Reaction performed for 48 h reaction time. [c]Reaction performed for 72 h.

was found that both the size and the position of an ester group in the starting pyrone ring **1** were of key importance for the reaction effectiveness and selectivity. The use of *tert*-butyl coumalate **1b** resulted in decreased reactivity, as longer reaction time (48 h) was required to achieve full conversion. Product **6n** was obtained with good yield and enantioselectivity and poor diastereoselectivity. Moreover, the reaction with pyrone **1c** containing an ester group in the C3 position provided **6o** with significantly lower diastereo- and enantioselectivity for both diastereoisomers.

The usefulness of the cycloadducts obtained was demonstrated in selected transformations (Scheme 3). Initially, decarboxylative retro-Diels−Alder reaction was attempted (Scheme 3, top). It was found that the reaction proceeded

Scheme 3. Diastereoselective Transformations of [2.2.2]-Bicyclic Lactone 4 or 6



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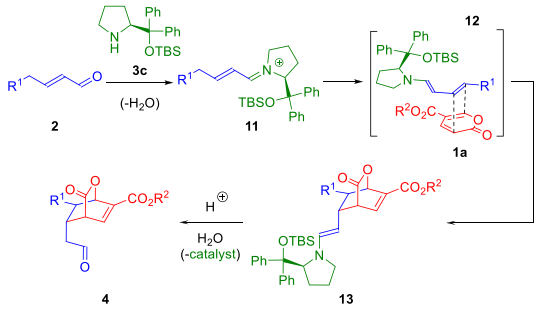
Org. Lett. 2020, 22, 1813−1817

efficiently at high temperature in the presence of catalytic amounts of PTSA. Interestingly, the initially formed product **7** underwent spontaneous intramolecular Diels–Alder cycloaddition to give interesting polycyclic system **8** containing an additional cyclobutane ring.[6a] It was also found that when the original cycloadduct **4a** was subjected to the condensation with phenylhydrazine, the originally formed phenylhydrazone **9** underwent intramolecular 1,3-dipolar cycloaddition to give **10** as the final product (Scheme 3, bottom).[10] The transformation proved possible to perform in a one-pot fashion without the need to isolate any of the intermediates. Notably, both developed processes proceeded in a diastereoselective manner providing **8** and **10** as single diastereoisomers (for the assignment of relative configuration, see the Supporting Information).

The absolute configuration of the products was unequivocally confirmed by single crystal X-ray analysis of the [2.2.2]-bicyclic lactone **6l** (for details, see the Supporting Information).[11] Configuration of the remaining products **6a–k,m–o** was established by analogy. Based on the configurational assignments, the reaction mechanism was proposed (Scheme 4). It was initiated through the dienamine **12** formation in a

Scheme 4. Asymmetric Synthesis of [2.2.2]-Bicyclic Lactones 4: Mechanistic Considerations



sequence involving condensation of **2** with **3c** and subsequent γ-deprotonation. **12** acted as a dienophile in a subsequent all-carbon IEDDA cycloaddition with **1a** utilized as an electron-poor diene. Notably, *E,E*-**12** reacted in its *s-cis* conformation, presumably due to favorable secondary orbital interactions. With the formation of enamine **13** accomplished, its protonation and subsequent hydrolysis took place, regenerating the catalyst **3c** and affording **4** as a final product.

In conclusion, we have developed a novel approach to [2.2.2]-bicyclic lactones. It utilized an aminocatalytic inverse-electron-demand Diels–Alder reaction between α,β-unsaturated aldehydes and coumalates. It proceeded through the intermediacy of the corresponding dienamine with its distal double bond acting as the dienophile in the reaction. Target products were subjected to selected transformations indicating their high functionalization potential.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00138.

Experimental procedures, characterization of the products, NMR data, and HPLC traces (PDF)

Accession Codes

CCDC 1963626 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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All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was realized within the Opus programme (Grant Number: 2016/23/B/ST5/01927) from the National Science Centre, Poland. Thanks are expressed to Dr. Lesław Sieroń (Faculty of Chemistry, Lodz University of Technology) for performing X-ray analysis.

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Org. Lett. 2020, 22, 1813−1817