

Research Article

Organocatalytic Cascade Reaction of Aliphatic Enals and Benzoylnitromethane: Synthesis of Enantioenriched Tetrasubstituted Cyclohexene Carbaldehyde

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A new example of the reactivity of enals with benzoylnitromethane was studied in a Michael-Michael-Aldol-Dehydration quadruple organocascade reaction. The reaction unexpectedly yielded a tetrasubstituted cyclohexene carbaldehyde with excellent enantiomeric excess when crotonaldehyde was used as the Michael-acceptor, whereas using (*E*)-Hex-2-enal as the Michael-acceptor formed a cyclic hemiacetal by steering the reaction into the intramolecular formation of the same intermediate via a Michael-Heterocyclization domino reaction.

1. Introduction

The design of synthetic strategies that result in highly functional and stereoselective organic compounds with consecutive stereocenters obtained through cascade reactions [1–11] are of great use in asymmetric synthesis as precursors of high added value molecules [12–14]. Cascade reactions are defined as “two or more bond-forming transformations which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step” [15]. In the literature, biocatalysis and organometallic catalysis have been described as strategies currently used to carry out these types of reactions [16–22].

However, organocascade reactions have played an important role in the efficient production of highly complex chemical structures [1, 23]. Organocatalysts are proline-sized organic molecules, often referred to as artificial enzymes, able to tolerate numerous functional groups and with the ability to be used under soft reaction conditions [1].

The latest advances in organocatalysis have demonstrated that the geometry of the iminium ion can be controlled in the stereoselective formation of carbon-carbon and carbon-heteroatom bonds [1, 11, 24–28]. Likewise, enamine activation has been shown to control the stereochemistry of alpha-functionalization of aldehydes and ketones with a variety of electrophiles [24, 29–31].

Based on previous examples, an important challenge in organocatalysis is the discovery of a simple organocatalyst able to promote stereoselective cascade reactions with high reaction yields. Studies have shown that these types of catalysts are suitable for the development of cascade reactions because they offer different, yet able to be combined, activation modes [13, 14, 23, 32]. The quadruple cascade reaction [9, 33–35] is one recently described example of the efficiency of organocatalysts in stereocontrolled cascade reactions, where it was possible to obtain structures with high structural complexity. An interesting example is the formation of Michael adducts and their subsequent intramolecular cyclization, promoting the formation of cycles with consecutive stereocenters, which can be used as

building blocks for more complex molecules. In this way, the influence of the pKa [36–40] of (pronucleophiles) is decisive in obtaining the type of product. For example, nucleophiles with pKa values of 9 used as Michael donors form Michael adducts that spontaneously cycle into hemiacetals via an intramolecular reaction [37], while nucleophiles with pKa of 10–14 lead to the formation of cyclic derivatives with a carbonyl function (Figure 1).

In the present investigation, organocatalysis and the influence of the pKa of benzoynitromethane (pronucleophile) were evaluated in the reaction with crotonaldehyde and (*E*)-Hex-2-enal as starting reactants for the formation of Michael adducts and their subsequent intramolecular cyclization, promoting the formation of cycles with consecutive stereocenters, which can be used as building blocks for more complex molecules. The results showed that in addition to pKa, the length of the alkyl chain of the unsaturated aldehyde is decisive for the type of cyclic system that can be obtained. The reaction conditions of the process were also studied and demonstrated that the reaction time is decisive in the formation of adducts.

2. Materials and Methods

2.1. General Experimental Information. IR spectra were recorded on a Thermo Fisher Scientific Nicolet iS10 FTIR spectrometer with a monolithic Diamond ATR accessory and absorption in cm^{-1} (Thermo Scientific, Waltham, MA, USA). ^1H and ^{13}C -NMR spectra were recorded at 400 MHz on a Bruker Avance 400 instrument. Chemical shifts are reported in ppm, using the solvent residual signal. Specific rotations were measured using a 1 mL cell with a 1 dm path length, and a sodium lamp, and concentrations are given in g/100 mL. Chiral HPLC analysis was performed using Daicel Chiralcel OD Columns (250 \times 4.6 mm). UV detection was monitored at 256 nm.

2.2. General Synthesis Method. Dichloromethane (10 mL), (R)—(+)— α , α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (Hayashi-Jørgensen catalyst) (15 mol%), and benzoic acid (cocatalyst) (15 mol%) were added to a solution of benzoynitromethane (0.10 mmol) and crotonaldehyde (0.30 mol). The reaction was carried out at room temperature under constant stirring until the reaction ended. The products were purified by column chromatography using a hexane-ethyl acetate mixture (95: 5). TLC analysis was carried out on aluminum-backed plates coated with silica gel 60 and an indicator F254, and the plates were visualized with UV light.

2.2.1. Synthesis of 4-Benzoyl-4-Nitro-3,5-Dipropylheptanedial. (3a) A colorless oil with a 15% yield was obtained in 6 h; ^1H NMR (400 MHz, CDCl_3) δ 9.97 (s ancho, 2H), 7.79–7.77 (m, 2H), 7.62–7.58 (m, 1H), 7.51–7.47 (m, 2H), 2.45–2.43 (m, 2H), 1.29–1.23 (m, 4H), 1.07 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H).

2.2.2. Synthesis of 5-Benzoyl-4,6-Dimethyl-5-Nitrocyclohex-1-Enecarbaldehyde. (3b) A colorless oil with an 18% yield was obtained in 6 h; $[\alpha]_D^{20}$ = +199 (c = 0.55, CHCl_3 , 96% ee) ^1H NMR (400 MHz, CDCl_3) δ 9.51 (s, 1H), 7.82 (dd, J = 8.4, 1.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.45 (brt, J = 8.4, 7.2 Hz, 2H), 6.80 (dd, J = 5.0, 2.6 Hz, 1H), 3.90 (q, J = 6.8 Hz, 1H), 3.00 (dp, J = 12.1, 6.2 Hz, 1H), 2.69 (dt, J = 20.7, 5.3 Hz, 1H), 2.02–1.93 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 192.5, 189.7, 147.4, 142.8, 134.6, 134.0, 129.2, 127.9, 99.8, 34.2, 31.0, 22.8, 17.3, 16.9; HPLC (Chiralcel OD-H hexane/EtOH = 98: 2, 1.0 mL/min, λ = 256 nm) t_R = 6.8 min (minor), t_R = 7.9 (major).

2.3. Synthesis of 3-(1-Nitro-2-Oxo-2-Phenylethyl) Hexanal. (3c) Dichloromethane (10 mL), (R)—(+)— α , α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (Hayashi-Jørgensen catalyst) (15 mol%) and benzoic acid (cocatalyst) (15 mol%) were added to a solution of benzoynitromethane (0.10 mmol) and (*E*)-Hex-2-enal (0.10 mol). The reaction was carried out at room temperature under constant stirring until the reaction ended. The products were purified by column chromatography using a hexane-ethyl acetate mixture (95: 5). TLC analysis was carried out on aluminum-backed plates coated with silica gel 60 and an indicator F254, and the plates were visualized with UV light.

A colorless oil with a 17% yield was obtained in 4 h; ^1H NMR (400 MHz, CDCl_3) δ 9.77 (t, J = 1.0 Hz, 1H), 8.13–8.10 (m, 2H), 7.63–7.59 (m, 1H), 7.50–7.45 (m, 2H), 4.44 (dd, J = 6.0, 1.0 Hz, 1H), 2.76–2.68 (m, 1H), 2.69–2.54 (m, 2H), 1.44–1.31 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H).

2.4. Synthesis of 2-Ethoxy-5-Nitro-6-Phenyl-4-Propyl-3,4-Dihydro-2H-Pyran. (3e) Dichloromethane (10 mL), (R)—(+)— α , α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (Hayashi-Jørgensen catalyst) (15 mol%) and benzoic acid (cocatalyst) (15 mol%) were added to a solution of benzoynitromethane (0.10 mmol) and (*E*)-Hex-2-enal (0.30 mol). The reaction was carried out at room temperature under constant stirring until the reaction ended. The products were purified by column chromatography using a hexane-ethyl acetate mixture (95: 5). TLC analysis was carried out on aluminum-backed plates coated with silica gel 60 and an indicator F254, and the plates were visualized with UV light.

A colorless oil with a 30% yield was obtained in 6 h; $[\alpha]_D^{20}$ = +2.8 (c = 0.65, CHCl_3 , 68% ee) ^1H NMR (400 MHz, CDCl_3) δ 8.10–8.05 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 6.18 (dd, J = 6.0, 4.0 Hz, 1H), 4.56 (dd, J = 12.3, 6.1 Hz, 1H), 4.37 (dd, J = 12.3, 7.2 Hz, 1H), 3.79 (dq, J = 9.5, 7.1 Hz, 1H), 3.62 (dq, J = 9.5, 7.1 Hz, 1H), 2.59–2.48 (m, 1H), 2.05–1.81 (m, 2H), 1.48–1.34 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.1, 133.4, 129.8, 129.7, 128.5, 97.3, 79.5, 79.3, 65.3, 36.0, 34.0, 33.2, 15.0, 13.9; HPLC (Chiralcel OD-H, hexane/EtOH = 95: 5, 1.0 mL/min, λ = 256 nm) t_R = 1.7 min (minor), t_R = 2.8 Min (major); IR (ATR/ cm^{-1}) 2928, 2257, 1715, 1550. 1379, 1271.

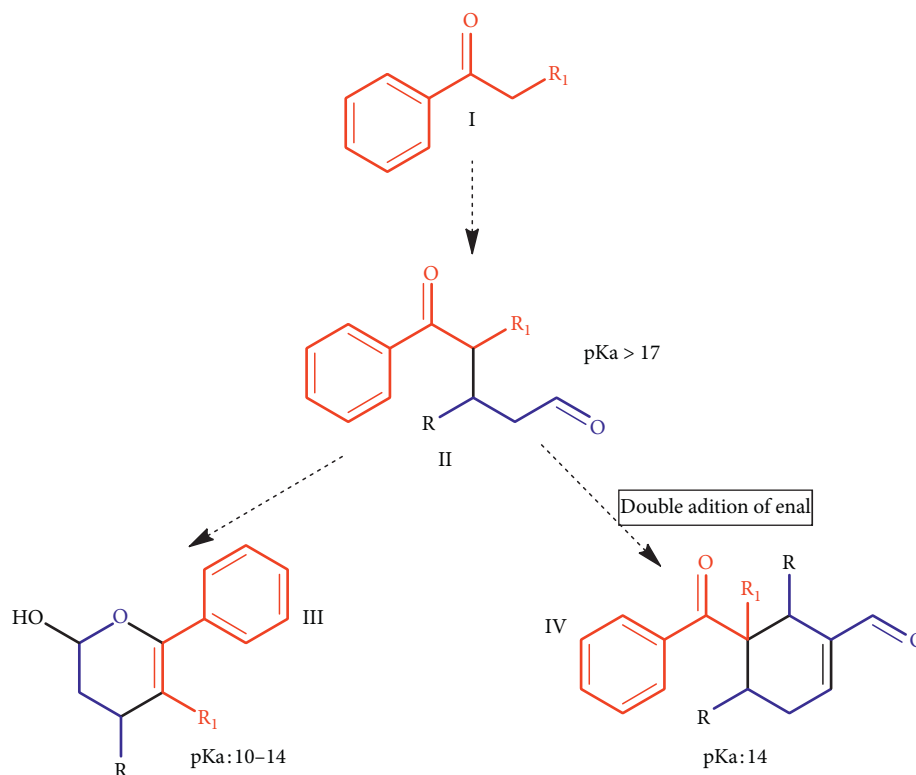


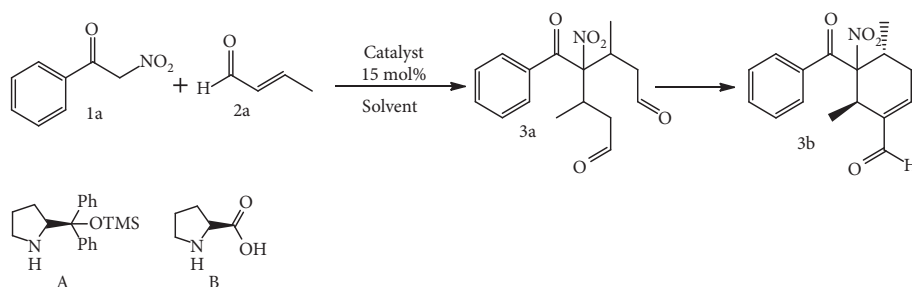
FIGURE 1: Possible structures that can be obtained by the Michael donor pKa value.

3. Results and Discussion

As mentioned above, for the present study, we chose benzonitromethane (1a) as the pronucleophile in the organocatalyzed Michael addition, which is an adequate model for the evaluation of the reaction conditions and the chirality that the process involves. Additionally, Crotonaldehyde and (*E*) Hex-2-enal were used as Michael-acceptor while (A) (R)—(+)- α , α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (otherwise known as the Hayashi-Jørgensen catalyst) and (B) proline were used as catalysts, where the latter served as a bi-functional catalyst activating both enals and nitroketones. The first step of the study involved the reaction between 1a and crotonaldehyde (2a), initially following the method as described in the literature [38]. TLC analysis of the reaction showed the formation of two products; these derivatives were purified by column chromatography and characterized via spectral techniques, including ¹H-NMR, ¹³C-NMR, and 2D-NMR experiments (see Supplementary Materials (available here)).

In this way, the first additional product of 1a with 2a showed that the ¹H-NMR spectrum displayed characteristic signals of aldehyde at 9.97 ppm and for alkyl chains signals at 0.96 and 1.07 ppm for methyl groups, 1.29 ppm for the methylene group, and for the methine group the signal was observed at 2.44 ppm. Aromatic protons were observed at 7.78, 7.60, and 7.49 ppm. The integral of these signals was for five protons in the aromatic ring, and for aldehyde, it was for two protons, indicating that the Michael addition reaction occurred with two molecules of the unsaturated aldehyde,

allowing the formation of adduct 3a (Scheme 1). The confirmation of this result is evident with the disappearance of the signals at 4.00–4.50 ppm, which confirmed the formation of the adduct. Unfortunately, this product was very unstable and could not be fully characterized. The second derivative, 3b, was obtained as a colorless and viscous liquid. The ¹H-NMR spectrum displayed downfield signals at 9.97 ppm, attributed to one proton of the aldehyde group, at 7.82, 7.59, and 7.45 ppm for the aromatic protons (integral for one aromatic ring) and at 6.80 ppm, which is a characteristic of a vinyl proton. In this sense, the decrease in the integral of the aldehyde signals is indicative of the formation of an unsaturated ring, which was confirmed with two groups of signals: first, the signals for diastereotopic protons of the methylene group in the cycle at 2.69 and 2.02 ppm, and second, the signal at 3.00 ppm. Finally, in the ¹H-NMR spectrum, the signal at 3.90 ppm was attributed to the methine in the cycle, which, coupled with the signal at 1.18 ppm, was attributed to the methyl group in the cycle. The ¹³C-NMR spectrum showed fourteen signals, which are expected to compound, from these displayed characteristic signals of ketone and aldehyde groups at 192.5 and 189.7 ppm, respectively. The aromatic carbons appeared at 127–134.6 ppm and the vinyl carbons at 147.4 and 142.8 ppm. In this way, the signal at 99.8 ppm confirmed the presence of a tetrasubstituted carbon linked to the nitro group, and the number of signals in the aliphatic region consisted of the structure of the unsaturated cycle (Scheme 1). Once the chemical identity of the majority products of the reaction was established, the best reaction conditions were evaluated (Table 1).



SCHEME 1: Reaction conditions screening for benzoylnitromethane-crotonaldehyde Michael addition.

TABLE 1: Influence of solvent, stoichiometric ratio, catalyst, and cocatalyst in the 1a to 2a Michael addition.

Entry	Catalyst	Solvent	Cocatalyst	Ratio	Time (h)	Yield (%) ^a	Ee% ^b
1	B	DCM	—	1 : 1	4	8	Nd
2	B	DCM	—	1 : 2	3	12	Nd
3	B	CHCl ₃	—	1 : 1	4	10	Nd
4	B	CHCl ₃	—	1 : 2	3	11	Nd
5	B	Hexane	—	1 : 1	10	No rxn	—
6	B	Toluene	—	1 : 1	10	No rxn	—
7	B	Et ₂ O	—	1 : 1	10	No rxn	—
8	B	EtOH	—	1 : 1	4	Complex mixture	—
9	B	DMSO	—	1 : 1	4	Complex mixture	—
10	A	DCM	Bac	1 : 1	7	25	93
11	A	DCM	Bac	1 : 2	6	30	93
12	A	DCM	Bac	1 : 3	6	40	96
13	A	CHCl ₃	Bac	1 : 1	6	20	90
14	A	CHCl ₃	Bac	1 : 3	6	30	92
15	A	DCM	—	1 : 3	19	35	80

^aYield refers to the isolated compound. ^bThe percentages were determined by chiral HPLC. All entries were carried out at room temperature

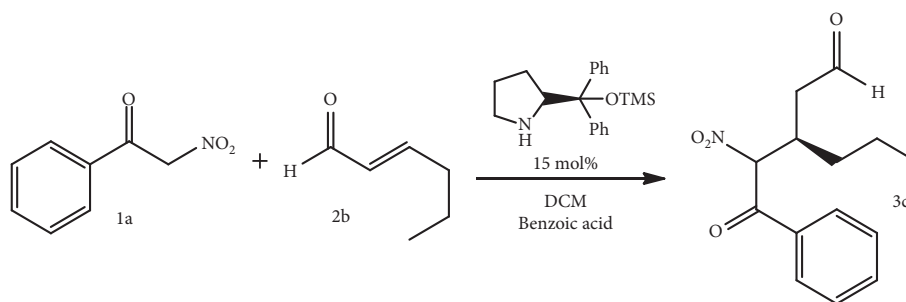
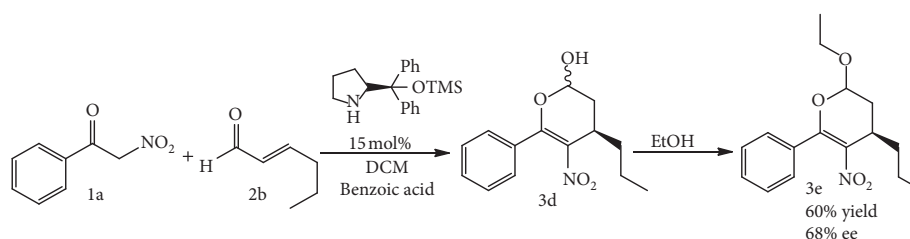
During the first set of trials, the influence of the solvent, catalyst, cocatalyst, and the stoichiometric relationship of the reactants were evaluated in order to pinpoint the necessary reaction conditions for obtaining high yields of product **3b**. Table 1 illustrates the most relevant results.

Results show that pairing catalyst B with most of the solvents used either resulted in complex mixtures or exhibited no reaction at all when examined with TLC. However, using catalyst B with halogenated solvents (entries 1 and 3, Table 1) yielded a majority of one product, which was later purified by column chromatography and identified as product **3b**. Based on these results, the influence of the stoichiometric ratio of reactants was studied next (entries 2 and 4, Table 1), where it was discovered that the reaction yield of product **3b** increased when the ratio of 2a was increased. Then catalyst A and cocatalyst BAc (benzoic acid) were paired only with the halogenated solvents. Entries 10–14, Table 1, show that the percentage yield of product **3b** and the rate of the reaction increased significantly. According to these results, the best reaction conditions for the formation of **3a** were determined to be those present in entry 12, Table 1. It is important to highlight the fact that this product is described in the literature as the first example where a cyclohexene carbaldehyde with consecutive chiral centers, one of which is a quaternary carbon center, was obtained via organocatalysis.

Once the reaction conditions were optimized, the reactivity of aliphatic enals such as 2b was evaluated in order to determine if the reaction could also be used with longer-chain enals. Surprisingly, the reaction did not occur as expected, since it yielded two different products (**3c** and **3d**) in 20 hours. Each product was isolated, but only **3d** was completely characterized (Schemes 2 and 3).

The first product of 1a with (*E*) Hex-2-enal (2b) is showed in the ¹H-NMR spectrum signals of the aliphatic chain at 0.92, 1.38, 2.63, and 2.72 ppm. The characteristic signal at 4.44 ppm was attributed to the hydrogen of the methine group attached to the nitro group. In addition, aromatic protons were observed in the region of 7.45–7.50, 7.59–7.63, and 8.10–8.13 ppm. Finally, the ¹H-NMR spectrum displayed characteristic signals of aldehyde at 9.97 ppm. In this way, the ratio of integrals between the aldehyde hydrogen and the five signals in the aromatic region indicated that Michael's additional reaction occurred with one molecule of the unsaturated aldehyde, and this is consistent with the signals of adduct **3c** (Scheme 2). In order to confirm the above assignments, the ¹H-¹H COSY spectrum was recorded. The correlations for **3c** are given in Table 2; the observed ¹H-¹H COSY correlations confirm the connectivity and the assignments made. Similarly to adduct **3a**, the stability of **3c** was not stable enough to characterize.

In order to characterize the product of the cyclization, the reaction was carried out for a longer period of time until

SCHEME 2: Formation of reaction intermediate **3c**.

SCHEME 3: Michael-heterocyclization-acetylation domino reaction.

TABLE 2: Correlations for compound Michael adduct **3c** in the COSY spectrum.

Proton	δ (ppm)	Correlation
1	0.92	2 (1.44–1.31)
2	1.44–1.31	1 (0.92), 2 (1.44–1.31), 4 (2.76–2.68)
3	2.69–2.54	4 (2.71), 9 (9.77)
4	2.76–2.68	2 (1.44–1.31), 3 (2.69–2.54), 5 (4.44)
5	4.44	4 (2.76–2.68)
6	7.50–7.45	7 (7.63–7.59), 8 (8.13–8.10)
7	7.63–7.59	6 (7.50–7.45)
8	8.13–8.10	6 (7.50–7.45)
9	9.77	3 (2.69–2.54)

TLC showed that product **3c** had disappeared from the reaction mixture. After 30 hours, **3b** had disappeared. Later, purification by column chromatography of the majority product was carried out. As shown in Table 3, signals of ^{13}C -NMR and ^1H -NMR were unambiguously assigned through 1D- and 2D-NMR experiments, including the HMQC and HMBC spectra. The ^{13}C -NMR spectrum shows a signal at 79.3 ppm with no correlation in the HSQC spectrum. In the HMBC spectrum, this signal shows a correlation with the methyl protons 4a, b (see Figure 2 and Table 3) at 1.81–2.05 ppm and with the signal at 2.50 ppm; hence these signals must be due to diastereotopic protons of CH_2 of the cyclic acetal ring. There is a weak signal at 166.1 ppm. This signal has no correlation with the HMQC spectrum and was attributed to vinyl carbon because of its connectivity with proton 8. In the HMBC spectrum, the signal at 33.2 ppm exhibits a correlation with the diastereotopic methylene group protons 7a and 7b at 4.37 and 4.56 ppm. An important piece of evidence of acetal formation can be seen in the HMBC spectrum through the signal at 97.3 ppm, which exhibits a correlation with the diastereotopic methylene

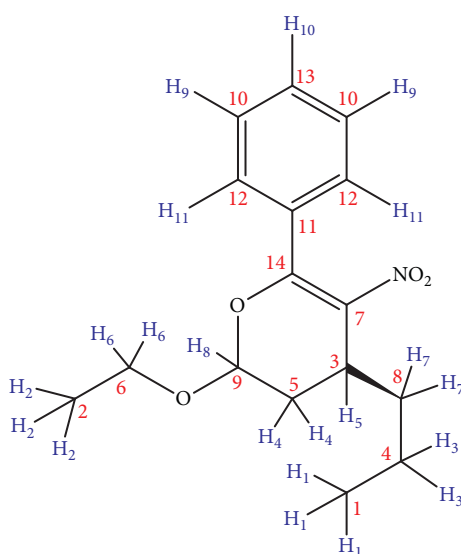
group protons at 1.81–2.05 ppm and the correlations with the proton (5) at 2.48–2.59 ppm.

Previous literature has mentioned this Michael addition product (**3c**) as a reaction intermediate, although not when nucleophiles like **1a** with pK_a values of 7.7 were used. This is attributable to the fact that increasing the acidity of the ketone's α -protons induces the spontaneous cyclization of the Michael adduct into cyclic hemiacetals or into 3-hydroxy-cyclohexanones [38]. Instances where the Michael adduct is stable and does not spontaneously cycle have been documented, but only when the pK_a of the ketone's α -protons remains close to 19, as described by [37, 39].

In order to characterize product **3c**, the reaction was carried out for a longer period of time until TLC showed that product **3b** had disappeared from the reaction mixture. After 30 hours, **3c** had disappeared, but upon purification by column chromatography, product **3d** decomposed. The literature states that nucleophiles with pK_a values of 9 used as Michael donors form Michael adducts that spontaneously cycle into hemiacetals via an

TABLE 3: Correlations for **3c** in the HSQC and HMBC spectra.

Carbon	δ (ppm)	Correlation HSQC	Correlation HMBC
1	13.9	1 (0.90)	3 (1.48–1.34)
2	15.0	2 (1.23)	6a (3.62), 6b (3.79)
3	33.2	5 (2.59–2.48)	3 (1.48–1.34), 4 a, b (2.05–1.81), 7a (4.37), 7b (4.56), 8 (6.18)
4	33.9	3 (1.48–1.34)	1 (0.90), 5 (2.59–2.48), 7a (4.37), 7b (4.56)
5	35.6	4 a, b (2.05–1.81)	5 (2.59–2.48), 7a (4.37), 7b (4.56)
6	63.3	6a (3.62), 6b (3.79)	2 (1.23), 8 (6.18)
7	79.3	—	4 a, b (2.05–1.81), 5 (2.59–2.48)
8	79.5	7a (4.37), 7b (4.56)	4 a, b (2.05–1.81)
9	97.3	8 (6.18)	4 a, b (2.05–1.81), 5 (2.59–2.48), 6a (3.62), 6b (3.79)
10	128.5	9 (7.47)	10 (7.59)
11	129.7	—	9 (7.47), 11 (8.10–8.05)
12	129.8	11 (8.10–8.05)	9 (7.47), 10 (7, 59)
13	133.4	10 (7.59)	11 (8.10–8.05)
14	166.1	—	8 (6.18), 11 (8.10–8.05)

FIGURE 2: Structure and assignment of the proton and carbon signals of compound **3c**.

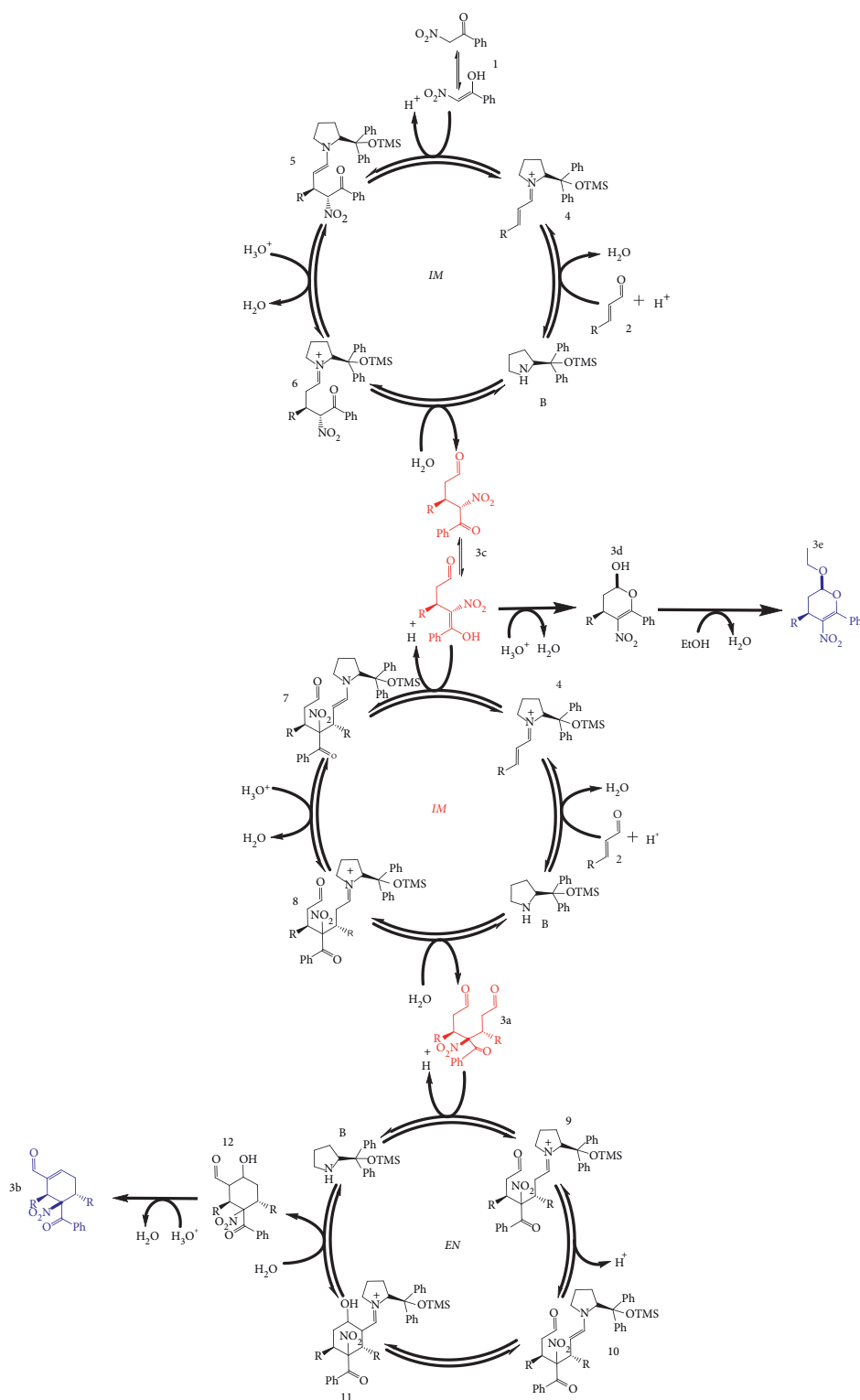
intramolecular reaction [37]. These studies have shown that these adducts should be oxidized or reduced in situ into pyranone or pyran derivatives, respectively, in order to avoid the compound's hydrolysis in the reaction medium. In the present project, ethanol was used as the nucleophile to form the alkyl derivative **3e** in order to stabilize and therefore be able to quantify and elucidate the structure of **3d** (Scheme 3).

Activation of the enal and the addition of the nucleophile follow the general path previously described by [41–44]. This means that the stereochemistry of the final product is dictated by the β -attack of the nucleophile from the less-hindered Re-face of the iminium ion.

Synthesis of product **3b** is described as a Michael-Michael-aldol-dehydration quadruple domino reaction. The first addition on the α -carbon by **2a** occurs via the iminium ion. Once the monoadduct is obtained, the second Michael addition by an additional **2a** molecule immediately takes place, obtaining **3a**. Additionally, during this secondary catalytic cycle by activation via

iminium ion, the monoadduct becomes an enolizable nucleophile. This secondary cycle yields **3a** (Scheme 4). Subsequently, this diadduct enters another cycle started off by an intramolecular aldol reaction prompted by enamine activation. Then condensation of **3a** and **B** generates an iminium ion **9** which tautomerizes into enamine **10**. Next, the enamine **10**'s α -carbon attacks its carbonyl carbon, yielding the cyclic intermediate **11**. The hydrolysis of this intermediate forms aldol product **12**, which, as described in the literature [13, 27], undergoes rapid dehydration prompted by **Bac**, finally yielding compound **3b**.

On the other hand, the synthesis of **3c** is described as a Michael-heterocyclization-acetalization domino reaction that involves activation modes via the iminium ion through the same intermediate reaction towards the formation of product **3b** (Scheme 3) (Scheme 4). However, this catalytic cycle does not undergo the double Michael addition that resulted in **3a**, allowing instead the isolation and purification of Michael monoadduct **3c**.



SCHEME 4: Proposed mechanism for the organocatalytic synthesis of 3a, 3b, 3c, 3d, and 3e.

This intermediate reacts intramolecularly, yielding hemiacetal **3d** by a 1,2-addition-mediated heterocyclization. Finally, due to the hemiacetal's instability in the one-pot reaction medium **3e** was generated by the addition of ethanol.

4. Conclusions

Based on background information related to organocatalytic domino reactions, especially those involving Michael additions featuring the use of ketones with active hydrogens as

nucleophiles, it was established that using a nucleophile with pKa values of 7.7, such as benzoylnitromethane, yields intermediate Michael adducts that, depending on the number of carbon atoms of the enal used, form a tetrasubstituted cyclohexene carbaldehyde with an excellent enantiomeric excess as a product of a Michael-Michael-aldol-dehydration quadruple cascade reaction when crotonaldehyde is used as the enal. Concurrently, when (*E*)-Hex-2-enal is used as the enal, the reaction occurs via a Michael-heterocyclization-acetylation domino reaction with a moderate enantiomeric excess. Moreover, as expected, the results show the effectiveness of a ketone with pKa values of 7.7 as the Michael donor, which contrasts with the higher pKa values reported in the literature.

Data Availability

The characterization data used to support the findings of this study are summarized within the article tables. In addition, the Supplementary Materials include the spectral data of the compounds.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Materials

The supplementary information features IR-FT, ¹H NMR, ¹³C-NMR, COSY, HSQC, HMBC spectra of the synthesized compounds and chromatograms of **3b** and **3e** with their respective ee calculation. (*Supplementary Materials*)

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