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NHC-Catalyzed Enantioselective Synthesis of Tetracyclic δ-Lactones by (4 + 2) Annulation of *ortho*-Quinodimethanes with Activated Ketones

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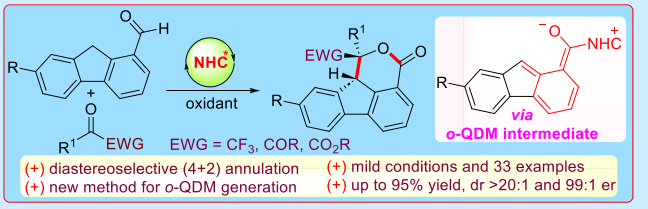
ABSTRACT: The N-heterocyclic carbene (NHC)-catalyzed generation of *ortho*-quinodimethanes (*o*-QDMs) from 9*H*-fluorene-1-carbaldehydes followed by the interception with activated ketones resulting in the enantioselective synthesis of tetracyclic δ-lactones is presented. High diastereoselectivity of products, remote C(sp^3)−H functionalization, broad substrate scope, and mild reaction conditions are the notable features of the present (4 + 2) annulation.



The efficacy of N-heterocyclic carbenes (NHCs) as potential organocatalysts is well-demonstrated by providing a unique mode of activation leading to versatile reactivity.[1,2] A distinctive spectrum of NHC-bound nucleophilic intermediates including Breslow intermediates (the key for benzoin and Stetter reactions),[3,4] homoenolates (conjugate umpolung),[5] and azolium enolates[6] have been generated from the corresponding aldehydes using the various activation strategies. A large collection of carbocycles and heterocycles could be synthesized by intercepting the carbene-bound intermediates with electrophiles.[2] In 2011, Ye and co-workers extended the azolium enolate chemistry in a vinylogous fashion via the generation of NHC-bound azolium dienolate equivalents.[7] The NHC-dienolates are subsequently trapped by activated ketones to form dihydropyranones. After Ye's pioneering work, numerous studies have surfaced regarding the generation and utilization of azolium dienolates from diverse carbonyl precursors.[8] One of the significant discoveries in this field is the use of *ortho*-quinodimethanes (*o*-QDMs) as an azolium dienolate source for the functionalization of benzylic carbon of aromatic aldehydes.[9]

o-QDMs, a highly reactive diene category, could be employed in various annulation reactions giving access to a wide range of benzannulated carbocycles and heterocycles.[10] In 2013, Chi and co-workers reported an elegant strategy for the generation of heterocyclic *o*-QDM intermediates from *o*-methyl heteroaryl aldehydes, which could undergo (4 + 2) annulation with activated ketones.[11] This strategy, however, failed for benzenoid analogues because the corresponding *o*-QDM intermediate is unlikely to form due to the enhanced aromaticity of the benzene ring. In 2016, the Glorius group demonstrated the NHC-catalyzed generation of *o*-QDM intermediate employing *ortho*-bromomethyl benzaldehydes, and the reaction afforded 1-isochromanone derivatives by using activated ketones as electrophiles (Scheme 1, method **I**).[12] Simultaneously, Rovis and co-workers established the asymmetric version of this strategy using NHC/Brønsted acid cooperative catalysis.[13] In 2018, the Chi group reported that NHCs could trigger the activation of the remote C−Si bond of 2-[(trimethylsilyl)-methyl]benzoate leading to the generation of the NHC-bound *o*-QDM intermediates via the cleavage of the C−Si bond in the presence of a fluoride source (method **II**).[14] The above-mentioned strategies, however, have limitations in terms of atom-economic generation of *o*-QDMs because these techniques demand the elimination of a leaving group to produce this pivotal intermediate.

Independent of the discovery made by the Chi group, Yao and co-workers documented another strategy for the NHC-catalyzed generation of *o*-QDM intermediates from 2-methyl-3,5-dinitrobenzoic acid in a racemic fashion (method **III**).[15] Despite the advancement of diverse annulation approaches,[16] the field of asymmetric reactions utilizing the atom-economic generation of NHC-bound *o*-QDM intermediates remained underdeveloped. Recently, Zheng and co-workers developed the enantioselective synthesis of dihydroisoquinolinones via the interception of the *o*-QDM intermediates with cyclic sulfonic imines (method **IV**).[17] But this methodology necessitates the presence of an electron-withdrawing group at the benzylic position to facilitate the generation of NHC-bound *o*-QDMs. Considering the potential applications of *o*-QDMs in the synthesis of a broad spectrum of benzannulated

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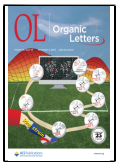
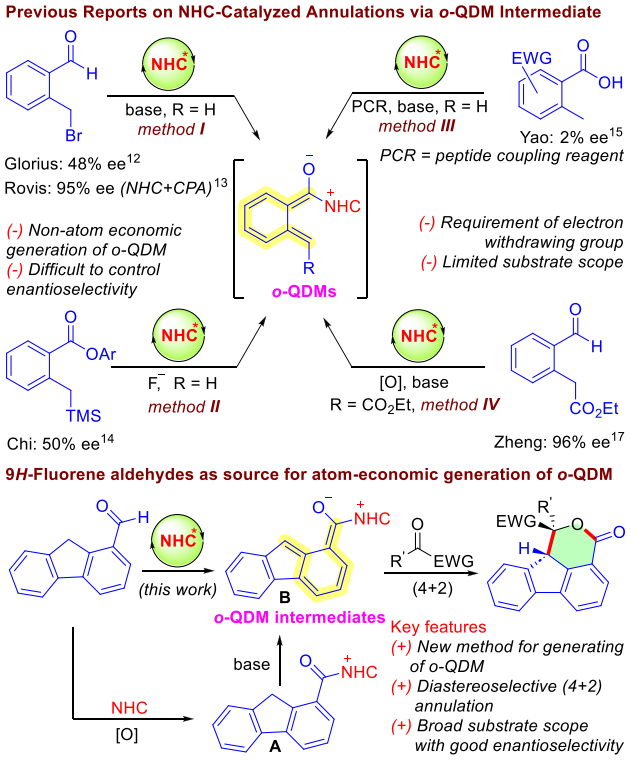


Scheme 1. NHC-Catalyzed Annulations via *o*-QDMs

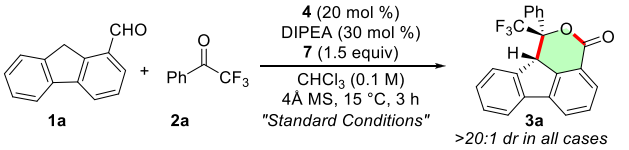


frameworks, the development of a rapid and efficient enantioselective approach is highly desirable.

In this context, we envisioned an alternative for the generation of *o*-QDM intermediates using 9*H*-fluorene-1-carbaldehyde derivatives.[18] The NHC-bound acylazolium **A** generated from 9*H*-fluorene-1-carbaldehyde in the presence of chiral NHC and an external oxidant could undergo γ-deprotonation to produce the key *o*-QDM intermediate **B**, which could undergo a (4 + 2) annulation with activated ketones (Scheme 1). The enhanced acidity of the benzylic proton of 9*H*-fluorene-1-carbaldehyde can be explained due to the enhanced aromatic character of the fluorenyl anion generated after deprotonation. Herein, we report the diastereoselective and enantioselective (4 + 2) annulation of 9*H*-fluorene-1-carbaldehyde with activated ketones for the synthesis of tetracyclic dihydro-indenoisochromenone derivatives.

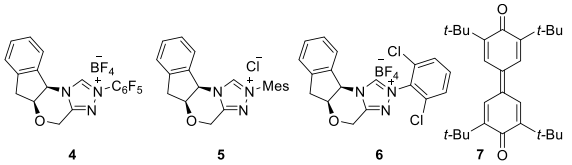
The optimization studies began by treating 9*H*-fluorene-1-carbaldehyde **1a** with 2,2,2-trifluoro-1-phenylethan-1-one **2a** in the presence of the carbene generated from the triazolium salt **4** using DIPEA in $CHCl_3$ along with 4 Å MS additive at 15 °C. Delightfully, after 3 h of stirring under these conditions, the desired tetracyclic δ-lactone **3a** was formed in 84% isolated yield and 95:5 er with excellent diastereoselectivity of >20:1 (Table 1, entry 1). In comparison to the NHC produced from **4**, the other common chiral carbene precursors **5** and **6** were inefficient in catalyzing this (4 + 2) annulation (entries 2, 3). The reaction performed without 4 Å MS provided lower reactivity and selectivity indicating the role of the additive in this reaction (entry 4). According to a rapid screening of several bases and solvents, DIPEA turned out to be the optimal base, and $CHCl_3$ was the best solvent for this annulation (entries 5−10). The reaction conducted at 25 °C instead of 15 °C furnished the tetracyclic δ-lactone **3a** in a lower yield and er

Table 1. Studies on Reaction Condition Optimization[a]



entry	variation of the standard conditions[a]	yield of **3a** (%)[b]	er[c]
1	*none*	85 (84)	95:5
2	**5** instead of **4**	<5	-nd-
3	**6** instead of **4**	13	75:25
4	without 4 Å MS as additive	35	90:10
5	DBU instead of DIPEA	77	80:20
6	Cs_2CO_3 instead of DIPEA	<5	-nd-
7	KO*t*-Bu instead of DIPEA	<5	-nd-
8	THF instead of $CHCl_3$	48	76:24
9	toluene instead of $CHCl_3$	75	88:12
10	CH_2Cl_2 instead of $CHCl_3$	75	84:16
11	25 °C instead of 15 °C	70	90:10
12	10 mol % of **4** instead of **20**	68	93:7
13	6 h instead of 3 h	78	95:5
14	1.0 equiv of **1a** and 1.5 equiv of **2a**	46	88:12

[a]Standard conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), **4** (20 mol %), DIPEA (30 mol %), $CHCl_3$ (0.1 M), 4 Å MS (50 mg), 15 °C, 3 h. [b]The ^{1}H NMR yield of the crude products is provided (using 1,3,5-trimethoxybenzene as the internal standard). The yield of isolated **3a** was provided in brackets. [c]Analyzed by HPLC analysis on a chiral stationary phase.



value (entry 11). Additionally, reducing the catalyst loading to 10 mol % resulted in the lowering of reactivity (entry 12). Extending the reaction time to 6 h as well as reversing the stoichiometry of **1a** and **2a** also did not help to improve the reactivity and selectivity (entries 13, 14).[19]

After identifying the optimized reaction conditions, then the scope and constraints of the present (4 + 2) annulation have been investigated. The effect of substituents on the aryl ring of 2,2,2-trifluoroacetophenone was initially explored (Scheme 2). Differently substituted 2,2,2-trifluoroacetophenone derivatives with electron-donating and -neutral groups at the 4-position of the aryl ring exhibited good compatibility under the present NHC-catalyzed annulation resulting in the formation of the desired dihydro-indenoisochromenone derivatives in moderate to good yields with good enantiomeric ratios and high diastereomeric ratios (**3a**−**3h**). Additionally, 2,2,2-trifluoroacetophenones bearing substituents at the 3-position and 2-position of the aromatic ring were also well tolerated, providing the corresponding tetracyclic δ-lactones in good yields and er values as a single diastereomer (**3i**−**3l**). The structure and stereochemistry of the 3-Me derivative **3j** was confirmed by the single crystal X-ray analysis.[20] Notably, 2,2,2-trifluoroacetophenones bearing disubstitution at the various positions of the aromatic ring also underwent smooth (4 + 2) annulation affording the desired products in good yields and with good stereoselectivities (**3m**−**3r**). Moreover, the 3,4,5-trimethoxy substituted α,α,α-trifluoroacetophenone worked well and furnished the desired product (**3s**) in 75% yield with 96:4 er

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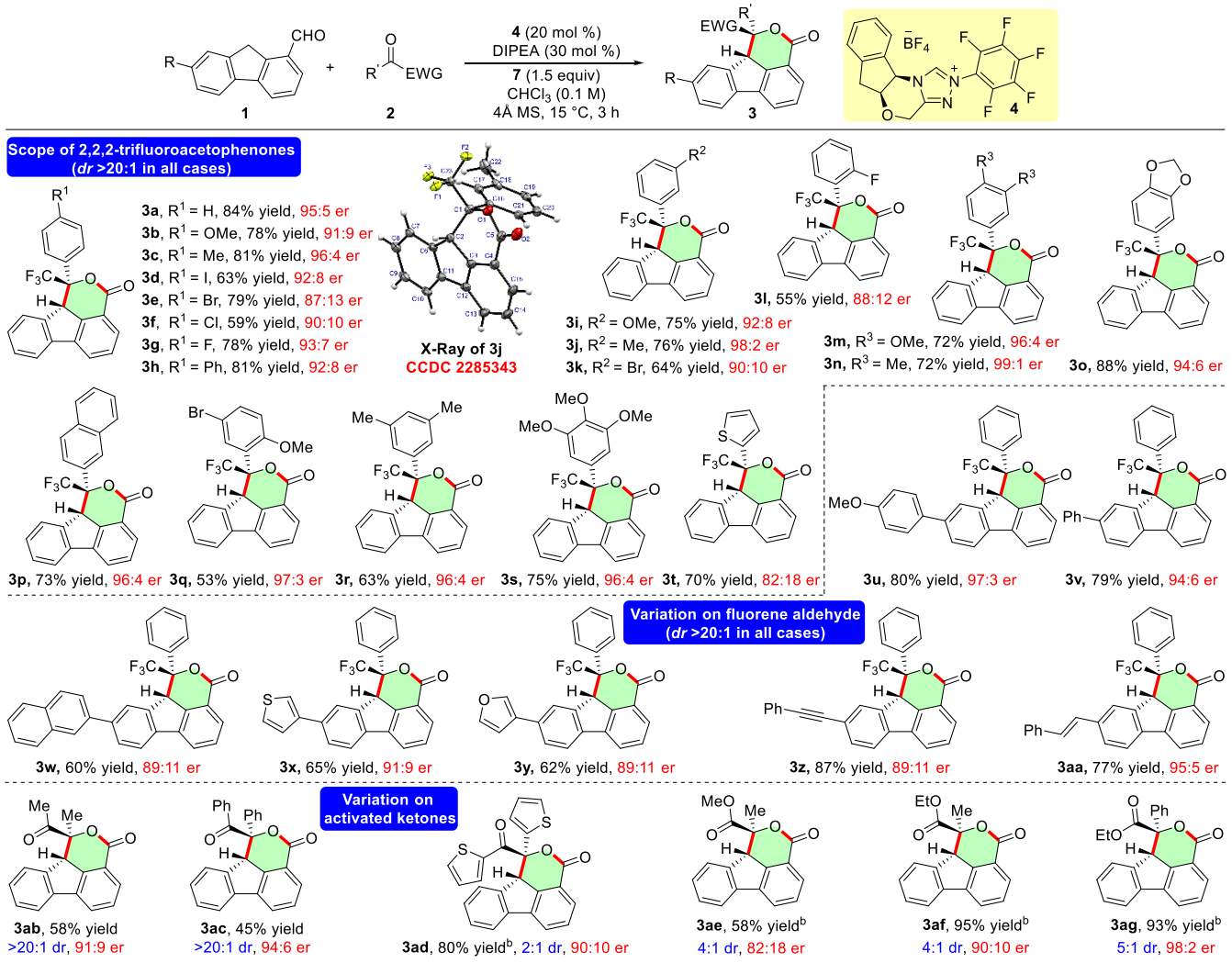
Org. Lett. 2023, 25, 7852−7857

Scheme 2. Substrate Scope of the NHC-Catalyzed (4 + 2) Annulation of Fluorene Aldehydes and Activated Ketones[a]



[a]General conditions: **1** (0.3 mmol), **2** (0.2 mmol), **4** (20 mol %), DIPEA (30 mol %), 7 (0.3 mmol), 4 Å MS (100 mg), $CHCl_3$ (0.1 M), 15 °C, 3 h. Isolated yield and er of major diastereomer are provided. The dr value was determined by ^{1}H NMR spectroscopy prior to purification. The HPLC analysis on a chiral stationary phase was performed to determine the er values. [b]Total yield of both diastereomers provided.

and >20:1 dr. The heteroaryl substituted $-CF_3$ ketone also did not affect the reaction outcome and provided the product **3t** in 70% yield with moderate er value.

Subsequently, the tolerance of the present methodology was studied employing differently substituted fluorene aldehydes. The *para*-methoxy phenyl and phenyl group at the 7-position of the aromatic ring of 9*H*-fluorene-1-carbaldehyde were well tolerated leading to the formation of the desired dihydro-indenoisochromenone derivatives in good yields and er values with high diastereoselectivities (**3u**, **3v**). Additionally, fluorene aldehydes bearing 2-naphthyl, 3-thienyl, and 3-furyl groups at the 7-position also provided the corresponding tetracyclic *δ*-lactones in reasonable yields with good er values (**3w**−**3y**). Moreover, the fluorene aldehydes containing alkynyl and alkenyl moieties at the 7-position were also compatible for this NHC-catalyzed (4 + 2) annulation furnishing the desired products in good yields and selectivities (**3z**, **3aa**).

The variation of the activated ketone was subsequently evaluated. When biacetyl and benzil were used as the activated ketone component, the respective products **3ab** and **3ac** were formed in moderate to good yields with good er and >20:1 dr. The reaction performed using 2,2′-thenil afforded the product **3ad** in 80% yield, 2:1 dr, and 90:10 er. Instead of 1,2-diketones, *α*-ketoesters can also be used as the electrophilic coupling partner in this (4 + 2) annulation, and the desired tetracyclic *δ*-lactones are formed in good yields and selectivities (**3ae**−**3ag**). Preliminary studies performed using *N*-methyl isatin substrate afforded the desired spiro-products in moderate yields as a mixture of diastereomers under the present conditions.[21]

This (4 + 2) annulation is easily scalable in a 1.0 mmol scale thus demonstrating the practicality of the present methodology. The reaction furnished **3a** in 83% yield, >20:1 dr, and 95:5 er (Scheme 3, eq 1). To gain insight into the role of the fluorenyl moiety in forming the *o*-QDM intermediates, a reaction was performed using 2-benzyl benzaldehyde **8a** as a substrate under the optimized reaction conditions (Scheme 3, eq 2). Interestingly, desired benzo-fused *δ*-lactone **9a** was not formed. It is reasonable to assume that the envisioned *o*-QDM intermediate **C** formed from **8a** has no stabilizing effect owing to the lack of a five-membered ring, which could provide aromatic stabilization. In the case of *o*-QDM intermediate **B**,

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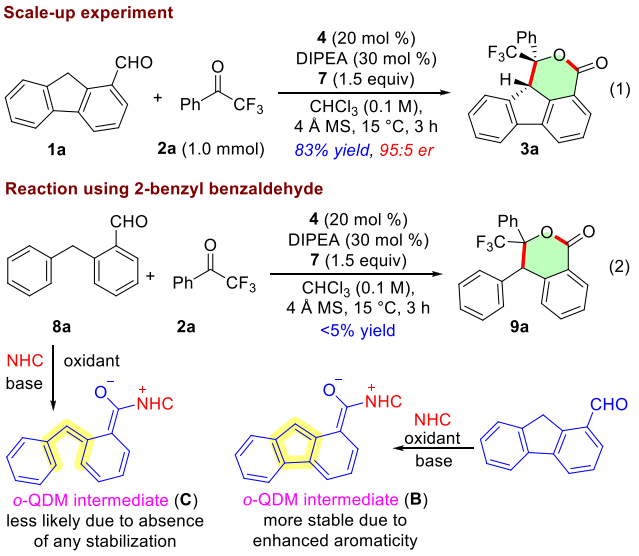
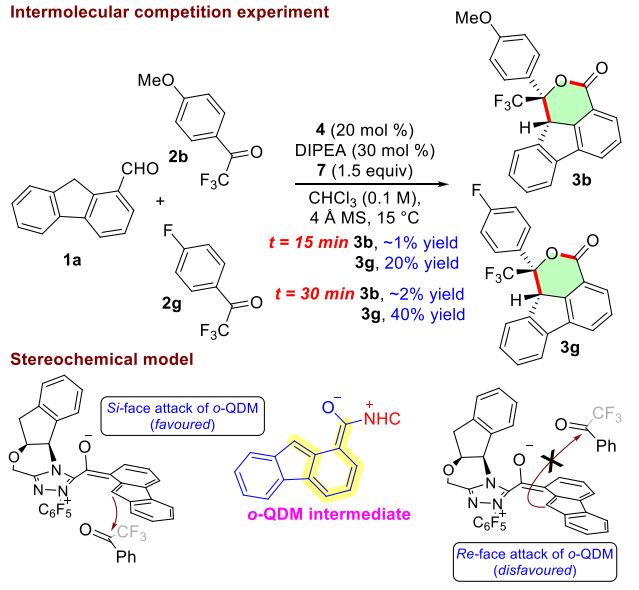
Scheme 3. Scale-up Experiment and Reaction Using 2-Benzyl Benzaldehyde



the formation of the cyclopentadienyl moiety could be a driving force for the stabilization.

To shed light on the reactivity difference between electronically different 2,2,2-trifluoroacetophenones, an intermolecular competition experiment was performed. Thus, an intermolecular competition experiment carried out between **2b** and **2g** under the optimized reaction conditions (quenching the reaction mixture after 15 and 30 min respectively) revealed that the 4-F substituted ketone **2g** reacts ∼20 times faster than the 4-OMe substituted ketone **2b** (Scheme 4). This is an indication that the relatively electron-rich ketones react slowly with the NHC-bound *o*-QDM intermediates due to the less electrophilic nature of the carbonyl group. Moreover, a plausible stereochemical model was proposed to explain the mode of addition of *o*-QDMs to the activated ketones. The

Scheme 4. Competition Experiment and Stereochemical Model



chiral NHC-bound *o*-QDM intermediate has two enantiotopic faces to intercept the electrophilic activated ketones. The above *Re*-face attack was disfavored due to the steric bulk offered by the chiral aminoindanol core of the catalyst, and hence the nucleophilic attack to the activated carbonyl likely proceeds from the bottom *Si*-face of the *o*-QDM intermediate.[22]

In conclusion, NHC-catalyzed enantioselective (4 + 2) annulation of 9*H*-fluorene-1-carbaldehydes with 2,2,2,-trifluoroacetophenones is demonstrated. Mechanistically, the reaction proceeds via the generation of chiral NHC-bound *o*-QDM intermediates, which undergo a (4 + 2) annulation to afford indenoisochromenone derivatives in good to excellent yields and good stereoselectivities. The strategy could be further explored for α-diketones and α-keto ester derivatives as the electrophilic coupling partner, demonstrating the generality of this present annulation. Mild conditions, broad substrate scope, and a new method for the generation of *o*-QDM intermediate are the notable features of this methodology.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03076.

Full details of experimental procedures, characterization data including the HPLC traces of all tetracyclic δ-lactones, and the X-ray data of **3j** (PDF)

Accession Codes

CCDC 2285343 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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(20) CCDC 2285343 (**3j**).

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