Organic & Biomolecular Chemistry



COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *Org. Biomol. Chem.*, 2024, **22**, 7128

Received 7th August 2024, Accepted 13th August 2024 DOI: 10.1039/d4ob01313a

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Catalytic stereoselective synthesis of cyclopentanones from donor-acceptor cyclopropanes and in situ-generated ketenes†

A dual $InBr_3$ -EtAlCl₂ Lewis acidic system was found to be optimal for promoting the diastereoselective (3 + 2)-cycloaddition of donor-acceptor cyclopropanes with *in situ*-generated ketenes to form cyclopentanones. The desired products were formed in good to excellent yields (70–93% for 16 examples) and with good to excellent diastereoselectivity and enantiospecificity.

Cyclopentanones and their derivatives, such as cyclopentan-1,3-diols, serve as vital structural components in various naturally occurring prostaglandins and pharmaceutical analogues like PGE₂ and bimatoprost. Notable pharmaceuticals including loxoprofen, donepezil, lubiprostone, and premarin also feature the cyclopentanone motif. However, current approaches to cyclopentanone synthesis often encounter limitations, particularly in achieving the desired 2,3-disubstituted or 2,3,4-trisubstituted cyclopentanone structures with sufficient substituent versatility and high diastereoselectivity. Most available catalytic technologies facilitate the direct preparation of only 2-substituted, 3-substituted, 2,4-disubstituted, and 3,4-disubstituted cyclopentanones, highlighting the need for more efficient and versatile synthetic strategies. ²

In seminal work, Johnson and co-workers demonstrated that Lewis acid catalysis could be employed to promote the (3 + 2)-cycloaddition of donor-acceptor (DA) cyclopropanes with aldehydes to access tetrahydrofurans with excellent enantiospecificity, enantioselectivity and diastereoselectivity.^{3,4}

A few years ago, our group and Lu's group independently reported that Pd(0)-catalyzed (3 + 2)-cycloaddition of vinylcyclopropanes with ketenes could afford highly substituted tetrahydrofurans.⁵ Shortly after, as part of a program on the development of new reactions of ketenes, we reported the dual Lewis acid-catalyzed (3 + 2)-cycloaddition of DA cyclopropanes with

A drawback of our 2019 methodology was the need to use pre-generated stable ketenes that are considered technically difficult to work with.⁶ Furthermore, the reaction diastereoselectivity was at a moderate level (dr up to 3:1). In this paper we describe the development of an efficient methodology for the synthesis of cyclopentanones from *in situ*-generated ketenes and readily available DA cyclopropanes.¹⁰ The current method significantly improves on prior reports of cyclopenta-

Scheme 1 Literature precedent and this work.

disubstituted ketenes to form cyclopentanones 3a (Scheme 1).⁶ Werz's group later showed that ketenedithioacetals could undergo (3 + 2)-cycloaddition with DA cyclopropanes under Lewis acid catalysis to access dithiaspiro compounds, which were then elaborated to substituted cyclopentanones, albeit with modest diastereoselectivity.⁷ In 2022, Studer and coworkers demonstrated that related cycloalkanes (bicyclo[1.1.0]-butane ketones) could also undergo Lewis acid-catalysed reaction with disubstituted ketenes to access bicyclo[2.1.1]hexane-2-ones.⁸ Recently, Punniyamurthy's group proposed the involvement of a vinyl ketene intermediate in the synthesis of bicyclic cyclopentapyrans from 2,4-dienals and DA cyclopropanes.⁹

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[†] Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob01313a

none synthesis from ketenes/ketene surrogates in that it caters for unstable, in situ-generated ketenes, without any need for prior isolation or purification.^{7,10} Moreover, the desired products are obtained with generally good to excellent diastereoselectivity (dr up to 37:1). Efficient transfer of chirality from starting enantioenriched cyclopropanes to cyclopentanone products was also verified.

We began our studies by exploring the reaction of in situgenerated methylketene 2a (generated in situ through reaction of propionyl chloride 4a with i-Pr2NEt) with phenyl-substituted donor-acceptor cyclopropane 1a in CH2Cl2 (Table 1). A range of Lewis acids were investigated including the dual Lewis acidic system (InBr3-EtAlCl2) we had previously determined to be optimal for reactions of disubstituted ketenes (Table 1). Reactions were found to proceed most effectively and cleanly at -78 °C. At higher temperatures, such as at -25 °C and at rt, no desired cyclopentanone product was formed and ketene dimerization was competitive. Solvents other than CH₂Cl₂, such as BTF and THF, were also investigated but led to no desired product being formed. Other reaction parameters that were found to be critical included order of addition of reagents (acyl chloride, amine base and cyclopropane). The dual Lewis acidic system of InBr₃-EtAlCl₂ was found to give the best results in terms of yield of the desired cyclopentanone (Table 1, entries 4 and 5), although other In(III) salts also functioned well in combination with EtAlCl₂ (Table 1, entries 6 and 7).

The need to use excess EtAlCl₂ (up to 2.5 equiv for optimal yields of 3c) was surmised to be due to quenching/protonation of the co-catalyst by some of the ammonium chloride salt produced by in situ ketene generation. Further optimization, carried out in parallel, demonstrated the need to employ excess mole equivalents of acyl chloride and i-Pr2NEt to

Optimization of synthesis of cyclopentanone: Lewis acids

| Entry | Lewis acid catalyst (mol%) | Lewis acid Co-catalyst (mol equiv) | Yield ^a [%] |
|-------|----------------------------|---------------------------------------|---------------------------|
| 1 | InBr ₃ (30) | _ | 0 |
| 2 | $InBr_3$ (30) | $EtAlCl_2$ (0.5) | 21 |
| 3 | $InBr_3$ (30) | $EtAlCl_2$ (1.0) | 35 |
| 4 | InBr ₃ (30) | $EtAlCl_2(2.5)$ | 79 |
| 5 | InBr ₃ (50) | $EtAlCl_2(2.5)$ | 81 |
| 6 | $InCl_3$ (30) | $EtAlCl_2$ (2.5) | 71 |
| 7 | $In(OTf)_3$ (30) | $EtAlCl_{2}$ (2.5) | 69 |
| 8 | $Sn(OTf)_3$ (30) | $EtAlCl_{2}$ (2.5) | 65 |
| 9 | $Cu(OTf)_3$ (30) | $EtAlCl_2$ (2.5) | 42 |
| 10 | CuI (30) | $EtAlCl_{2}$ (2.5) | 53 |
| 11 | FeCl ₃ (30) | $EtAlCl_2$ (2.5) | 0 |
| 12 | $InBr_3$ (30) | i-Bu ₂ AlCl (2.5) | 61 |

^a Isolated yield after flash column chromatography through silica gel. dr was $\geq 3:1$ in all cases.

Table 2 Optimization of synthesis of cyclopentanone: variation of reactant mole equivalents

| Entry | Propionyl chloride ^a (mol equiv) | i-Pr ₂ NEt ^a (mol equiv) | Yield ^b [%] | |
|----------------|---|---|---------------------------|--|
| 1 ^c | 1.0 | 1.2 | 12 | |
| 2^c | 3.0 | 3.2 | 54 | |
| 3^d | 3.0 | 3.2 | 0 | |
| 4^c | 5.0 | 5.2 | 90 | |

^a Mol equivalents calculated with respect to the starting cyclopropane derivative. b Isolated yield after flash column chromatography through silica gel. dr was $\geq 6:1$ in all cases. ^c i-Pr₂NEt was added to a solution containing the acyl chloride 4a and Lewis acids, followed by slow addition of cyclopropane 1b solution to the reaction solution (see ESI†). ^d i-Pr₂NEt was added to a solution of cyclopropane **1b**, acyl chloride 4a, InBr₃ and EtAlCl₂.

achieve optimal yields of 3d (Table 2, entries 1-4). Conventional in situ ketene generation through slow addition of propionyl chloride to a solution containing an amine base and other reagents was found to be completely unsuccessful. Only after addition of the amine to a solution containing the acyl chloride and Lewis acids, followed by slow addition of the cyclopropane solution to the reaction solution, were good results obtained (Table 2, entries 2 and 4 versus entry 3).

Optimization of diastereoselectivity in the formation of the cyclopentanone was then pursued. We quickly determined that exposure to silica during silica gel purification led to an increase in stereoselectivity, favouring the trans-isomer. To amplify the equilibration process, all crude products were stirred with silica gel in CH2Cl2 for 2 h at 50 °C prior to column chromatographic purification, leading to an increase in *trans*-diastereroselectivity (e.g. from 3:1 to 31:1 for 3i).

Having determined that the dual Lewis acidic system of InBr₃-EtAlCl₂ afforded the best results in terms of yield and diastereoselectivity of the desired cyclopentanone, we proceeded to evaluate the scope of the reaction methodology (Table 3).

Variation of ketene structure was investigated with methylketene, ethylketene, n-propylketene and benzylketene all giving good results in terms of yield of cyclopentanone product from cyclopropane 1b (Table 3, entries 2-5). 10,11 Differences in diastereomeric ratio noted with these ketenes may have been due to isomerization not having gone to completion during 2 h in some cases. Changes in the cyclopropane substitutent (R²) generally did not have a negative impact on diastereoselectivity, with aryl groups bearing electron donating or withdrawing substituents (entries 1 vs. 7 and 8) working equally well. 12,13 Heteroaromatic substituents also worked well (entries 10 and 11). A heteroatom substituent (N-phthaloyl, entry 12) directly bonded to the cyclopropane ring at the

Table 3 Substrate scope of (3 + 2)-cycloaddition

| Entry | \mathbb{R}^1 | \mathbb{R}^2 | \mathbb{R}^3 | Yield a [%] | Dr^b | Compound |
|-------|----------------|---------------------------|----------------|----------------|-----------------|------------|
| 1 | Et | Ph | Me | 79 | 9:1 | 3 c |
| 2 | Bn | Ph | Me | 90 | 33:1 | 3d |
| 3 | Bn | Ph | Et | 88 | 4:1 | 3e |
| 4 | Bn | Ph | n-Pr | 93 | 17:1 | 3f |
| 5 | Bn | Ph | Bn | 74 | 7:1 | 3g |
| 6 | Me | Ph | Me | 65 | 3:1 | 3h |
| 7 | Et | $4\text{-FC}_6\text{H}_4$ | Me | 79 | 31:1 | 3i |
| 8 | Et | $4-MeOC_6H_4$ | Me | 81 | 26:1 | 3j |
| 9 | Et | Styrenyl | Me | 70 | 5:1 | 3k |
| 10 | Et | 2-Furyl | Me | 83 | 13:1 | 31 |
| 11 | Et | 2-Thienyl | Me | 74 | 37:1 | 3m |
| 12 | Et | N-Phthaloyl | Me | 42 | 9:1 | 3n |
| 13 | Bn | Vinyl | Me | 81 | 17:1 | 30 |
| 14 | t-Bu | Vinyl | Me | 59 | 3:1 | 3р |
| 15 | i-Pr | Vinyl | Me | 68 | 6:1 | 3q |
| 16 | Et | Vinyl | Me | 71 | $4:1^c$ | 3r |
| 17 | Me | Vinyl | Me | 56 | 14:1 | 3s |

^a Isolated yield after flash column chromatography through silica gel.
^b dr was determined by ¹H NMR analysis of crude after silica gelmediated isomerization.
^c Not subjected to isomerization.

2-position also performed quite well. There was an influence of the ester group substituent on diastereoselectivity, with Me and Bn (\mathbb{R}^1) (entries 13 and 17) found to be superior to *t*-Bu and i-Pr (entries 14 and 15).

Additionally, it was determined that when enantioenriched **1b** (99% ee, (R) or (S)-**1b**) was used as the substrate that a specific enantiomer of **3d** was formed with high enantiomeric excess (96–98% ee), demonstrating the highly enantiospecific nature of the reaction (Scheme 2). Similar results were also observed for formation of enantioenriched **3c** (see ESI†).

Finally, reduction of 3d using NaBH $_4$ was found to proceed with optimal chemoselectivity (compared to DIBAL-H,

Scheme 2 Enantiospecificity of the reaction.

Scheme 3 Reduction and scale-up reactions.

Scheme 4 Proposed reaction mechanism.

L-selectride and CBS reagent) to provide the desired alcohol **5d** (68%) with modest diastereoselectivity (dr 2:1) (Scheme 3). Scale-up of the cyclopentanone synthesis was also explored and was found to afford the desired product **3d** in 92% yield and with a dr of 28:1 on a 2.6 mmol scale (producing 1.05 g of **3d**).

We propose that the reaction proceeds through a concerted asynchronous transition state (Scheme 4).3,6 InBr₃ is expected to activate the donor-acceptor cyclopropane and weaken the C-C bond between C₁ and C₂ in the transition state.³ EtAlCl₂ is proposed to activate the ketene and enable it to undergo reaction with the DA cyclopropane. 14,15 Addition of cyclopropane C_1 to the ketene carbonyl in stereoselective fashion (i.e. adjacent to the sterically smaller H substituent) with attack of the ketene α-carbon to C₂ of the cyclopropane leads to cyclopentanone formation. Activation by EtAlCl₂ is essential to the success of the reaction as in its absence, no desired product is formed (Table 1, entry 1). Alternatively, EtAlCl₂ may act by bonding to a bromide ligand in InBr3, thus increasing the Lewis acidity of the In(III) catalyst (Lewis acid-assisted Lewis acidity).16 Regardless, equilibration to provide the trans-isomer as the major diastereomer occurs under the reaction conditions (in the presence of excess base and Lewis acid). Further isomerization to achieve synthetically useful levels of diastereoselectivity (generally ≥8:1) was achieved after exposure to silica in CH₂Cl₂ (2 h at 50 °C).

Conclusions

In conclusion, we have developed a synthesis of cyclopentanones from donor-acceptor cyclopropanes and *in situ-*generated ketenes, in good to excellent yields (up to 93%) and with generally good to excellent diastereoselectivity (dr up to 37:1) and enantiospecificity. Future studies will seek to develop a DyKAT variant of this reaction.

Author contributions

N. J. K. supervised the research; N. J. K., S. M. and M. M. conceived the idea; S. M., S. M. C., S. A., M. M. and M. P. carried out the synthetic experimental work and data acquisition. N. J. K. prepared the manuscript with contributions from S. A. and B. G. K. All authors approved the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Support has been provided by Science Foundation Ireland (18/IF/6301 to N. J. K.) and the Irish Research Council (GOIPD/2019/637 to S. M. and GOIPG/2023/4884 to S. A.). Open access funding provided by IReL.

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