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

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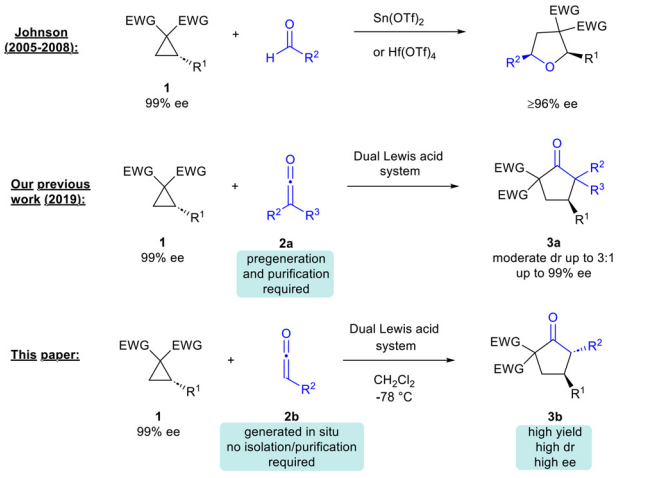
A dual $InBr_3$–$EtAlCl_2$ Lewis acidic system was found to be optimal for promoting the diastereoselective (3 + 2)-cycloaddition of donor–acceptor cyclopropanes with *in situ*-generated ketenes to form cyclopentanones. The desired products were formed in good to excellent yields (70–93% for 16 examples) 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 PGE_2 and bimatoprost.[1] Notable pharmaceuticals including loxoprofen, donepezil, lubiprostone, and premarin also feature the cyclopentanone motif.[1] 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 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 co-workers 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]

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.

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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 situ*-generated methylketene **2a** (generated *in situ* through reaction of propionyl chloride **4a** with i-Pr_2NEt) with phenyl-substituted donor–acceptor cyclopropane **1a** in CH_2Cl_2 (Table 1). A range of Lewis acids were investigated including the dual Lewis acidic system ($InBr_3$–$EtAlCl_2$) we had previously determined to be optimal for reactions of disubstituted ketenes (Table 1).[6] 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 CH_2Cl_2, 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 $InBr_3$–$EtAlCl_2$ 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 $EtAlCl_2$ (Table 1, entries 6 and 7).

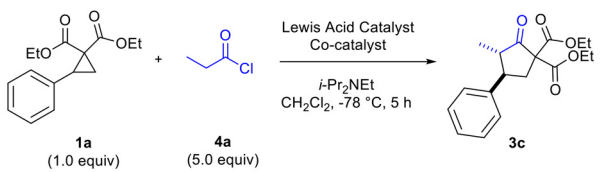
The need to use excess $EtAlCl_2$ (up to 2.5 equiv for optimal yields of **3c**) was surmised to be due to quenching/protonation of the co-catalyst by some of the ammonium chloride salt produced by *in situ* ketene generation. Further optimization, carried out in parallel, demonstrated the need to employ excess mole equivalents of acyl chloride and i-Pr_2NEt to 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 CH_2Cl_2 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 $InBr_3$–$EtAlCl_2$ 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 (R^2) 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

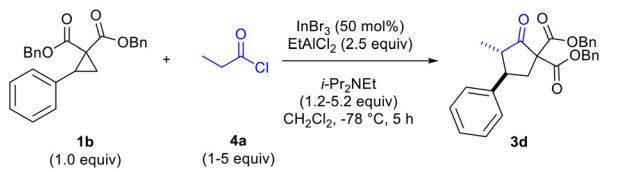
Table 1 Optimization of synthesis of cyclopentanone: Lewis acids



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_2AlCl (2.5)	61

[a] Isolated yield after flash column chromatography through silica gel. dr was ≥3 : 1 in all cases.

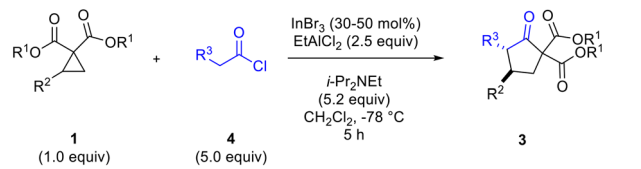
Table 2 Optimization of synthesis of cyclopentanone: variation of reactant mole equivalents



Entry	Propionyl chloride[a] (mol equiv)	i-Pr_2NEt[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 ≥6 : 1 in all cases. [c] i-Pr_2NEt 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-Pr_2NEt was added to a solution of cyclopropane **1b**, acyl chloride **4a**, $InBr_3$ and $EtAlCl_2$.

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



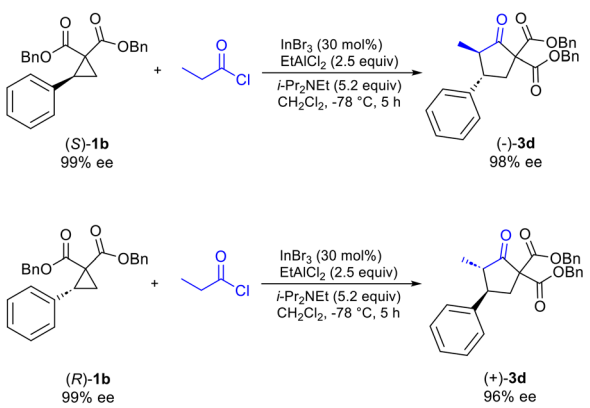
Entry	R^1	R^2	R^3	Yield[a] [%]	Dr[b]	Compound
1	Et	Ph	Me	79	9 : 1	**3c**
2	Bn	Ph	Me	90	33 : 1	**3d**
3	Bn	Ph	Et	88	4 : 1	**3e**
4	Bn	Ph	*n*-Pr	93	17 : 1	**3f**
5	Bn	Ph	Bn	74	7 : 1	**3g**
6	Me	Ph	Me	65	3 : 1	**3h**
7	Et	4-FC_6H_4	Me	79	31 : 1	**3i**
8	Et	4-$MeOC_6H_4$	Me	81	26 : 1	**3j**
9	Et	Styrenyl	Me	70	5 : 1	**3k**
10	Et	2-Furyl	Me	83	13 : 1	**3l**
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	**3o**
14	*t*-Bu	Vinyl	Me	59	3 : 1	**3p**
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 ^{1}H NMR analysis of crude after silica gel-mediated isomerization. [c] Not subjected to isomerization.

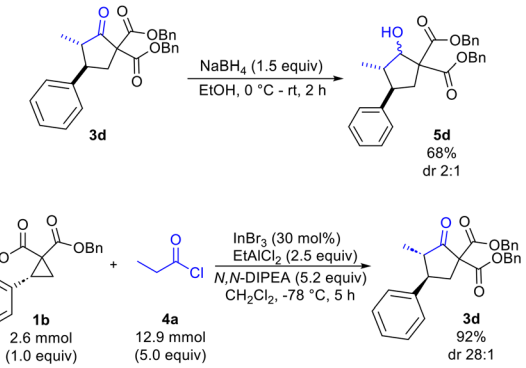
2-position also performed quite well. There was an influence of the ester group substituent on diastereoselectivity, with Me and Bn (R^1) (entries 13 and 17) found to be superior to *t*-Bu and i-Pr (entries 14 and 15).

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†).

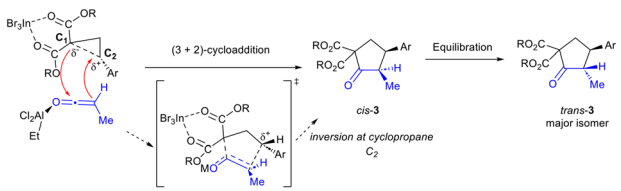
Finally, reduction of **3d** using $NaBH_4$ was found to proceed with optimal chemoselectivity (compared to DIBAL-H,



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] $InBr_3$ is expected to activate the donor–acceptor cyclopropane and weaken the C–C bond between C_1 and C_2 in the transition state.[3] $EtAlCl_2$ 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 C_2 of the cyclopropane leads to cyclopentanone formation. Activation by $EtAlCl_2$ is essential to the success of the reaction as in its absence, no desired product is formed (Table 1, entry 1). Alternatively, $EtAlCl_2$ may act by bonding to a bromide ligand in $InBr_3$, 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 CH_2Cl_2 (2 h at 50 °C).

Conclusions

In conclusion, we have developed a synthesis of cyclopentanones from donor–acceptor cyclopropanes and *in situ*-gener-

ated 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.

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