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Asymmetric Synthesis of Cyclopentanones through Dual Lewis Acid-Catalysed [3 + 2]-Cycloaddition of Donor-Acceptor Cyclopropanes with Ketenes

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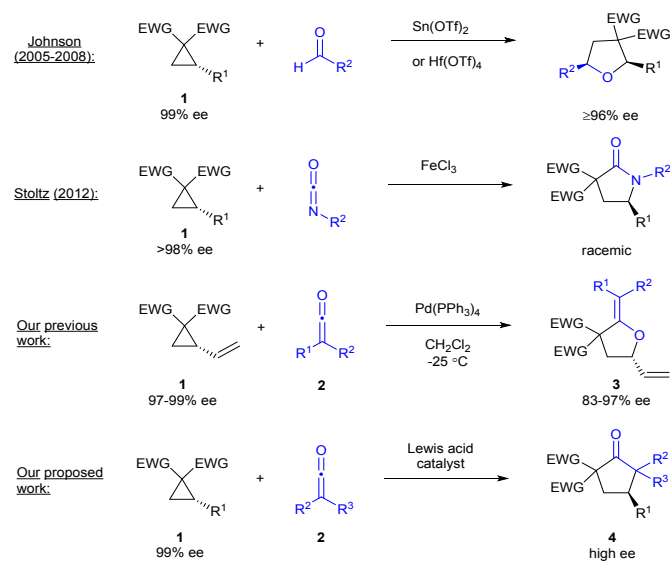
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When $\text{InBr}_3\text{-EtAlCl}_2$ (15-30 mol%) was used as a dual Lewis acid system to promote the formal [3 + 2]-cycloaddition of enantioenriched donor-acceptor cyclopropanes with ketenes, cyclopentanones were formed in good to excellent yields (84-99%, 18 examples), and with excellent transfer of chirality (15 examples, 90% ee to >99% ee).

Cyclopentanones and cyclopentanone derivatives (e.g. cyclopentan-1,3-diols) are important structural motifs that are found as components of many naturally occurring prostaglandins and pharmaceutically important prostaglandin analogues (e.g. PGE_2 , bimatoprost and latanoprost).¹ Other prominent cyclopentanone-containing pharmaceuticals include loxoprofen, donepezil, lubiprostone, and premarin.¹ However, the most widely employed methods for the synthesis of prostaglandin derivatives are characterized by lengthy approaches (8-10 steps) from the Corey lactone, which itself requires 3-9 steps to prepare.¹⁻³ We considered that a catalytic asymmetric synthesis of pivotal enantioenriched cyclopentanones from ketenes could provide a solution to the problem of developing more efficient syntheses of prostaglandin and cyclopentanone-containing pharmaceuticals (Scheme 1).

More broadly, there are limitations with many current methods for cyclopentanone synthesis in that rarely can the desired 2,3-disubstituted or 2,3,4-trisubstituted cyclopentanone structure, with adequate substituent versatility, be accessed in a direct and convergent fashion. Generally, only 2-substituted, 3-substituted, 2,4-disubstituted and 3,4-disubstituted

cyclopentanones can be prepared in a direct fashion using currently available catalytic technologies.⁴ The outstanding potential of a catalytic cyclopentanone synthesis methodology for pharmaceutical synthesis has therefore largely been untapped because of a lack of suitable methods.



Scheme 1. Precedent and proposed work.

In seminal work on catalytic [3 + 2] cycloadditions involving donor-acceptor (DA) cyclopropanes, Johnson's group had demonstrated that Lewis acid-catalysed [3 + 2] cycloadditions of DA cyclopropanes and aldehydes provided a diastereo- and enantioselective synthesis of tetrahydrofurans (Scheme 1).^{5,6} In recent years Stoltz's group had demonstrated that heterocumulene substrates (isothiocyanates and isocyanates) could be engaged in [3 + 2]-cycloadditions with DA cyclopropanes.⁷ But, a stoichiometric amount of Lewis acid reagent was required, and transfer of chirality was not consistently observed. Recently, our group and Lu's group independently demonstrated that Pd(0)-catalysed [3 + 2]-

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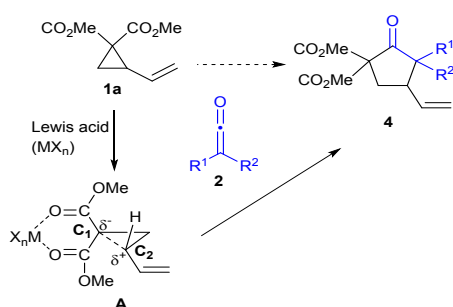
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cycloaddition of vinylcyclopropanes with ketenes could afford highly substituted tetrahydrofurans **3**.^{8,9} However, significantly, no general methodology describing [3 + 2] cycloadditions of DA cyclopropanes with ketenes to form cyclopentanones had emerged.⁸⁻¹¹ We proposed that a Lewis acid catalysed-[3 + 2] cycloaddition of DA cyclopropanes with ketenes would provide access to synthetically important cyclopentanone products (Scheme 2).^{10,12} Importantly, enantioenriched cyclopentanones would be accessed if the new methodology proceeded stereospecifically. This communication describes our efforts toward the development of an efficient methodology for the asymmetric synthesis of cyclopentanones from simple and readily available starting materials (ketenes and cyclopropanes).



Scheme 2. Proposed mode of catalysis.

The [3 + 2] cycloaddition of DA cyclopropane **1a** with methylphenylketene (and ethylphenylketene) was investigated (Table 1). Previously, we had determined that Pd(PPh₃)₄ catalysis had favoured formation of tetrahydrofuran **3** as the major product.⁸ Inspired by the work of Johnson's group we evaluated Lewis acids in order to influence a change in the regioselectivity of the formal [3 + 2] cycloaddition.⁵ To our delight the use of InBr₃ or Sn salts (Sn(OTf)₂ or SnCl₄) led to the desired cyclopentanone **4** (Table 1). Enantioenriched DA cyclopropanes were then prepared according to previously reported procedures and examined under the reaction conditions.¹³

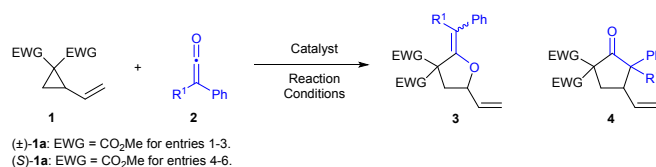


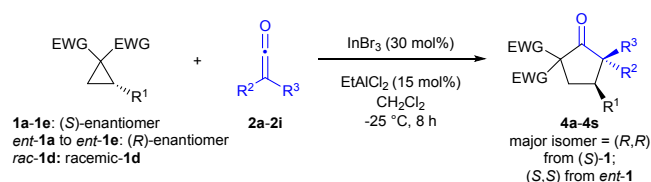
Table 1. Optimization of Lewis acid-catalysed formal [3 + 2]-cycloaddition.

Entry	R ¹	Conditions	Conv [%] ^a	3:4 ^b	dr ^b (4)	ee [%] ^c (4)
1	Me	CH ₂ Cl ₂ , rt, Sn(OTf) ₂ (20 mol%)	95	>1:99	1.2:1	-
2	Me	CH ₂ Cl ₂ , -25 °C, Sn(OTf) ₂ (10 mol%)	0	-	-	-
3	Me	CH ₂ Cl ₂ , rt, InBr ₃ (20 mol%)	85	>1:99	1.2:1	-
4	Et	CH ₂ Cl ₂ , rt, InBr ₃ (10 mol%)	75	>1:99	1.1:1	80
5	Et	CH ₂ Cl ₂ , -25 °C, EtAlCl ₂ (10 mol%)	40	>1:99	1.5:1	nd
6	Et	CH ₂ Cl ₂ , -25 °C, InBr ₃ (30 mol%), EtAlCl ₂ (15 mol%)	>99	>1:99	2:1	90

^a % conversion, determined by GC-MS analysis of crude product. ^b **3:4**, and ^c ee for major diastereomer determined by chiral HPLC analysis. (S)-**1a** (99% ee) employed.

4 was formed with unsatisfactory enantiomeric excess (70-80% ee) when (S)-**1a** (99% ee) was employed as DA cyclopropane starting material (entry 4). We suspected that the low stereochemical fidelity was due to racemization of cyclopropane **1a** under ambient conditions, and that carrying out the reaction at low temperature might lead to improved transfer of chirality.⁵⁻⁷ Recent work by Brown's group had shown that use of stoichiometric amounts of EtAlCl₂ could facilitate stereocontrol in the synthesis of cyclobutanones from disubstituted ketenes and alkenes.¹⁴ Subsequent experiments revealed that employment of an InBr₃-EtAlCl₂ catalytic system allowed reactions to proceed effectively at -25 °C. The new dual catalytic system provided optimal reaction conversion, diastereoselectivity, and transfer of chirality (90% ee, Table 1 entry 6).¹⁴ Me₂AlCl was also found to work equally effectively as EtAlCl₂. We then proceeded to apply the optimized reaction conditions involving the novel catalytic system to the synthesis of a range of cyclopentanones derived from different ketenes and DA cyclopropanes **1a-1e** (Table 2).

Employment of the dual system was found to be very effective with aryl-substituted DA cyclopropanes, as excellent transfer of chirality was observed in most cases (14 examples 92->99% ee).

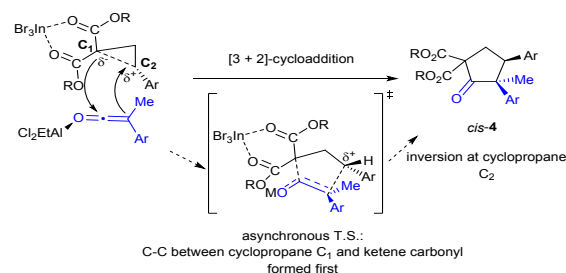
**Table 2.** Substrate scope.

Entry	1	EWG	R ¹	R ²	R ³	% yield ^a	% ee ^b	dr	4
1	1a	CO ₂ Me	C ₂ H ₅	Et	Ph	99	90	2:1	4a
2	1b	CO ₂ Me	Ph	Ph	Ph	54	58		4b
3	1c	CO ₂ Et	Ph	Et	Ph	99	98	2:1	4c
4	<i>ent-1c</i>	CO ₂ Et	Ph	Et	Ph	99	99	2:1	4d
5	<i>rac-1d</i>	CO ₂ Et	C ₂ H ₅ Ph	Me	Ph	86	-	2:1	4e
6	1e	CO ₂ Bn	Ph	Me	Ph	92 (63) ^c	>99	3:1	4f
7	<i>ent-1e</i>	CO ₂ Bn	Ph	Me	Ph	94 (62) ^c	99	3:1	4g
8	1e	CO ₂ Bn	Ph	Me	4-MeC ₆ H ₄	84	>99	3:1	4h
9	<i>ent-1e</i>	CO ₂ Bn	Ph	Me	4-MeC ₆ H ₄	87	99	3:1	4i
10	1e	CO ₂ Bn	Ph	Me	2-FC ₆ H ₄	87	>99	2:1	4j
11	<i>ent-1e</i>	CO ₂ Bn	Ph	Me	2-FC ₆ H ₄	90	>99	2:1	4k
12	1e	CO ₂ Bn	Ph	Me	4-CF ₃ C ₆ H ₄	84	92	3:1	4l
13	<i>ent-1e</i>	CO ₂ Bn	Ph	Me	4-CF ₃ C ₆ H ₄	88	92	3:1	4m
14	1e	CO ₂ Bn	Ph	Me	C ₆ H ₁₁	94	nd	2:1	4n
15	<i>ent-1e</i>	CO ₂ Bn	Ph	Me	C ₆ H ₁₁	92	nd	2:1	4o
16	1e	CO ₂ Bn	Ph	Et	Ph	88	98	3:1	4p
17	<i>ent-1e</i>	CO ₂ Bn	Ph	Et	Ph	91	98	3:1	4q
18	1e	CO ₂ Bn	Ph	<i>n</i> -Bu	Ph	92 (55) ^c	99	3:1	4r
19	<i>ent-1e</i>	CO ₂ Bn	Ph	<i>n</i> -Bu	Ph	94 (57) ^c	98	3:1	4s

^a Yield is isolated yield for both diastereomers. ^b ee for major diastereomer determined by chiral HPLC analysis. Enantioenriched cyclopropanes **1a-1e** (99% ee) were employed as starting material (see SI for full details). ^c Isolated yield of pure major diastereomer.

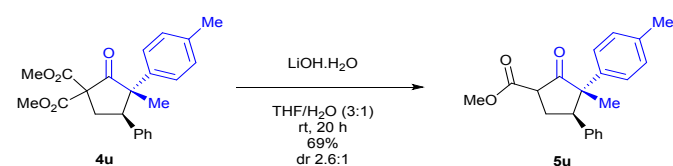
A range of ketenes (eight in all) such as methylphenylketene, ethylphenylketene, *n*-butylphenylketene, diphenylketene, *c*-hexylmethylketene, and a number of alkylarylketenes bearing electron donating or electron withdrawing groups on the aryl ring performed excellently, with the desired cyclopentanones being obtained in yields of 84-99% in most cases.¹⁵ The most difficult example involved diphenylketene, and resulted in cyclopentanone **4b** being formed in 58% ee. However, this result was superior to our prior results using In(III) or Sn(II)/Sn(IV) salts alone, where the desired cyclopentanone had been obtained as a racemate. Moderate to good

diastereoselectivity (dr 2:1 to 3.2:1) favoring formation of the *cis* (*syn*)-diastereomer was observed in most cases. A mild beneficial effect on diastereoselectivity was observed as the ester alkoxy-substituent was modified from methyl, to ethyl, and to benzyl, with a corresponding increase in dr from *ca.* 1.2:1 to >3:1 achieved. For many examples in Table 2, the product could be obtained as a single diastereomer in 50-65% isolated yield after a single flash column chromatographic purification (without additional re-purification of mixed fractions). For example, **4f** was obtained in 63% yield in diastereomerically and enantiomerically pure form after a single standard flash column chromatographic purification of the crude product. The absolute and relative stereochemistry was assigned based on X-ray crystal structure analysis of cyclopentanones **4u** and **4w** (see SI and cifs **4u** and **4w**).¹⁶ The relative stereochemistry of the major isomer was deduced to be *cis* and so all other cyclopentanone examples were assigned *cis*-relative stereochemistry by analogy. The absolute stereochemistry at C2 on DA cyclopropane **1** was found to undergo inversion during the formal [3 + 2] cycloaddition to give cyclopentanones **4** (see SI and cifs **4u** and **4w**), e.g. (*S*)-**1e** → (*R,R*)-**4r**.^{5,17}

**Scheme 3.** Possible mechanism for cyclopentanone formation.

A possible mechanism that would explain the observed absolute and relative stereochemistry is shown in Scheme 3. The reaction could proceed through an asynchronous cycloaddition mechanism whereby C₁ of the InBr₃-DA cyclopropane complex adds to the less sterically hindered side of the EtAlCl₂-activated ketene.^{5,14,17} The second C-C bond forming event would occur with inversion of stereochemistry at C₂ of the cyclopropane, before racemization can occur (cyclization onto C₂ must be faster than planarization at C₂), to provide *cis*-**4** as the major isomer.^{5,17}

Finally, the synthetic utility of a cyclopentanone product was investigated. Cyclopentanone **4u** was subjected to hydrolysis conditions and found to undergo methylester hydrolysis-decarboxylation to afford synthetically useful ketoester **5u** in good yield.

**Scheme 4.** Transformation of cyclopentanone.

In conclusion, we have developed a dual Lewis acidic In(III)-Al(III) catalytic system that provides access to enantioenriched cyclopentanones for the first time from donor-acceptor cyclopropanes and disubstituted ketenes. Future studies will further explore the concept of dual Lewis acid catalysis for the promotion of other cycloadditions of donor-acceptor substrates with cumulenes and heterocumulenes.¹²

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Conflicts of interest

There are no conflicts to declare.

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