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Effect of protic additives in Cu-catalysed asymmetric Diels–Alder cycloadditions of doubly activated dienophiles: towards the synthesis of magellanine-type *Lycopodium* alkaloids†

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Abstract

The pronounced beneficial effect of a precise amount of protic additive in an enantioselective Cu-catalysed Diels–Alder reaction is reported. This reaction, which employs a cyclic alkylidene β-ketoester as a dienophile, represents one of the first examples of a transformation where these extremely versatile, though highly unstable reaction partners participate effectively in catalytic asymmetric cycloaddition with a functionalised diene. The cycloadduct was used as an intermediate towards the synthesis of magellanine-type *Lycopodium* alkaloids featuring a Stille cross-coupling of a highly congested enol triflate and a unique Meinwald rearrangement/cyclopropanation sequence.

Alkylidene β-ketoesters feature prominently in the synthesis of complex natural products, due in part to their effectiveness as substrates for the formation of quaternary stereocenters.[1–3] In addition to being extremely reactive Michael acceptors in simple conjugate additions[3,4] and formal 2+2 cycloadditions,[5] their potential as dienophiles in Diels–Alder cycloadditions has been widely exploited, because of the ubiquity of the resulting hydrindane core in various classes of natural products when 5-membered cyclic analogs are used.[2] While many racemic and diastereoselective examples of Diels–Alder cycloadditions using alkylidene β-ketoesters as dienophiles have been reported, successful catalytic asymmetric variants remain scarce and typically lack generality with respect to the structure of the diene and dienophile.[6] Indeed, this subset of dienophiles is notoriously unstable to protic and Lewis acids, heat, and even simple dissolution in certain solvents, which has been attributed to their high propensity to polymerise following tautomerisation.[1,7] Since enantioinduction in catalytic asymmetric Diels–Alder reactions most often stems from the activation of the dienophile with a chiral Lewis or protic acid, the instability of cyclic

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Conflicts of interest

There are no conflicts to declare.

alkylidene β-ketoesters towards such catalysts has significantly impeded their use in these reactions. In addition to this inherent reactivity issue, the suppression of background (noncatalysed) reactions can also be challenging since the presence of geminal electron-withdrawing groups makes these dienophiles particularly reactive, even at low temperatures. In order to enable the development of a general catalytic asymmetric reaction with cyclic alkylidene β-ketoesters, it is therefore critical to identify a catalyst which activates the dienophile enough to outcompete the background reaction, while minimising its acidcatalysed decomposition. Since these dienophiles are capable of rigid two-point binding with bidentate Lewis acids, one particularly attractive class of chiral complexes that may be employed in their activation are Cu-bis(oxazolines) (Cu-BOX), which have been extensively used in asymmetric Lewis acid catalysis.[8] While this catalyst system was previously found to be suitable in terms of activating alkylidene β-ketoesters, the resulting asymmetric induction has remained low due to inefficient chiral projection on the distal reactive site of the dienophile (Fig. 1, A).[7a]

An elegant solution to this challenge was recently reported by Nakada and co-workers,[6d] where the ester moiety was replaced by an imide to afford a complex in which the substituents on the chiral oxazoline groups and the alkene of the dienophile are more proximal (Fig. 1, B). This relationship can be inferred on the basis of stereoinduction models of N-acryloyloxazolidin-2-ones commonly used in asymmetric Diels–Alder reactions.[9] In this model, the rigidity of the system is achieved by intramolecular hydrogen bonding between the imide NH and the carbonyl of the enone moiety. While this affords excellent asymmetric induction in Diels–Alder cycloadditions when the appropriate chiral bis(oxazoline) is employed, the synthesis of this dienophile and the additional steps required to install/cleave the imide auxiliary significantly impedes its practicality and general use in complex molecule synthesis.[2e] In order to address this unresolved issue, we envisioned that similar rigidification might be achieved directly from the ester if an intermolecular hydrogen bond could be established using a catalytic amount of a protic additive (R–OH, Fig. 1, C). Key to this hypothesis would be the requirement that the remaining binding site in the resulting complex is occupied by an added Lewis basic ligand (L) to disfavor complexation as found in A. Here, we report our studies towards the establishment of such a model in a catalytic asymmetric Diels–Alder cycloaddition using a cyclic alkylidene β-ketoester as dienophile in the presence of protic additives. Such additives were found to both accelerate the reaction and significantly improve the observed stereoselectivity, in accordance with a model such as C. The hydrindenone cycloadduct was employed as a key intermediate towards a synthesis of magellanine-type *Lycopodium* alkaloids. Given the versatility of the resulting hydrindenone products,[2] these initial forays into a general catalytic asymmetric Diels–Alder cycloaddition using cyclic alkylidene β-ketoesters should find broad applicability in the synthesis of complex natural products.

Our studies began with the evaluation of various non-catalysed reaction conditions between silyloxy diene 1 and dienophile 2 in order to identify a suitable medium where the background reaction would be suppressed (Scheme 1). As alluded to previously, dienophiles such as 2 are extremely reactive due to the presence of geminal electron-withdrawing groups, and so not surprisingly, complete conversion to the corresponding product (3) was

observed when the reaction was performed neat at room temperature for 20 hours (Scheme 1a).

With an eye towards applications in complex molecule synthesis, it should be noted that this reaction could be scaled up to produce 25 grams of 3 with similar efficiency.[10] The major diastereomer was identified by X-ray diffraction analysis of a single crystal to be the ester-*endo* product. We found that the rate of the reaction was highly dependent on concentration, and full suppression of the non-catalysed ('background') reaction could be achieved under dilute conditions at 0 1C (Scheme 1b).

With this information in hand, we evaluated the effect of solvent and protic additives on the efficiency of a potential stereoselective variant of the transformation (Table 1).

Preliminary studies indicated that the nature of the bis(oxazoline) ligand and the Cu salt counterion used had a significant impact on the stereoselectivity of the reaction, with 10 mol % $Cu(OTf)_2$ and 12 mol% *t*-Bu-BOX, a common combination in asymmetric Lewis acid catalysis,[8] affording the best initial results.[10,11] A striking feature of these reactions that we quickly observed was that the presence of water (*e.g.* using $Cu(OTf)_2$ stored open to the atmosphere), significantly accelerated the reaction. Indeed, very little conversion was observed after 3 h when carefully dried $Cu(OTf)_2$ was used in the absence of protic additives (see entries 1 and 6), while full conversion was observed in the presence of 10 mol% H_2O for most solvents evaluated (entries 2–5). While CH_2Cl_2 as solvent afforded virtually no enantiocontrol (entry 2), the use of slightly Lewis basic solvents afforded increased enantioselectivity, with Et_2O leading to the best enantiomeric ratio (entries 3–5). Notably, this observation is in accordance with our proposed model (see Fig. 1, C), suggesting that a Lewis basic ligand (L) is necessary to avoid bidentate complexation as in A, which would lead to poor enantioinduction because of inefficient relay of chiral information. It should be noted that strictly anhydrous conditions led to a comparable yield when *t*-Bu-BOX and $Cu(OTf)_2$ were pre-complexed for 16 h, albeit affording lower enantiocontrol (entry 7). This observation suggests that the rate acceleration observed in the presence of H_2O might be due to a faster ligand complexation event. Interestingly, using more than 10 mol% H_2O (1:1 Cu:H_2O ratio) had a detrimental effect on the efficiency of the reaction. Presumably, over-complexation to the chiral Cu complex occurs in this case precluding binding of the dienophile (entries 8 and 9). Other protic additives such as MeOH and i-PrOH were also found to have a similar effect, with MeOH affording a slightly better yield (compare entries 5 *vs*. 10 and entries 11 *vs*. 13). Lowering the polarity of the solvent by adding toluene improved both the yield and the stereoselectivity, and using the pure *E* isomer of diene 1 led to increased enantioselectivity, suggesting that the minor *Z* isomer was either reacting with poor stereocontrol or affording predominantly the opposite enantiomer (entries 11 and 12).[10] It should be noted that in all cases presented in Table 1, the main side-products of the reaction were identified as resulting from the acid-catalysed decomposition of diene 1 (3-methylbutenal isomers) or of dienophile 2, with the former side-reaction being mainly responsible for the moderate yields observed.

These optimised conditions readily translated to a larger scale, affording 1.75 mmol of enantioenriched hydrindenone 3 (Scheme 2). It was found that in order to conduct the

enantioselective cycloaddition reproducibly on scale, it was preferable to reduce the amount of dienophile 2 used to 2 equivalents and increase the catalyst loading to 15 mol%.

Hydrindenone 3 obtained from this enantioselective Diels–Alder reaction constitutes a framework commonly found in many biologically relevant natural products including alkaloids.[2] We envisioned that such a highly functionalised cycloadduct bearing three contiguous stereocenters could serve as an intermediate towards the synthesis of magellaninone, a tetracyclic *Lycopodium* alkaloid belonging to the fawcettimine class (Scheme 3).[12,13] Key to our synthetic strategy was masking the basic piperidine moiety present in the natural product as a pyridine. Towards this end, hydrindenone 3 was converted to the corresponding vinyl triflate, which was then employed in a Stille cross-coupling based on conditions developed by Corey.[14] This coupling efficiently led to pyridine 4, which contains all of the carbon atoms present in magellaninone. Reduction of the ester group in 4 to the primary hydroxyl and directed $VO(acac)_2$-catalysed homoallylic epoxidation led to epoxide 5 in good yield, the stereochemistry of which was unambiguously confirmed by X-ray crystallographic analysis. We envisioned using the epoxide moiety in 5 to introduce the requisite ketone group in the five-membered ring via a stereospecific Meinwald rearrangement,[15] which in turn could be transformed to a cyclopropylketone if an appropriate γ-leaving group was present. Considering the strain associated with such an intermediate, a subsequent vinylcyclopropane–cyclopentene rearrangement would directly lead to the functionalised tetracyclic core of magellaninone.[16] To set the stage for this sequence, the primary hydroxyl was transformed into a nucleofuge using Ts_2O and the TBS-protected secondary alcohol group was readily converted into the corresponding ketone *via* a deprotection/ oxidation sequence. Preliminary results indicated that the basicity of the pyridine needed to be further tempered in order for the Meinwald rearrangement to take place, due to the requirement of a strong Lewis acid. Therefore, the pyridine moiety was converted to the corresponding N-oxide using a methyltrioxorhenium-catalysed oxidation, which gave 6 in good overall yield. Extensive optimisation identified $Mg(OTf)_2$ as the ideal Lewis acid for the Meinwald rearrangement. At the high temperatures required for this transformation, the direct formation of cyclopropylketone 7 was observed in quantitative yield. Presumably, 7 arises from 6 as outlined in Scheme 3. This homoallylic epoxidation/ Meinwald rearrangement/cyclisation sequence is unprecedented and constitutes an expedient approach to the stereospecific formation of cyclopropylketones from homoallylic alcohols. While the vinylcyclopropane–cyclopentene rearrangement proved unsuccessful directly from 7, we anticipate that an intermediate such as pyridinium 8, readily obtained by a chemoselective reduction/methylation sequence, may provide an opportunity to rapidly access magellaninone following a final pyridinium reduction. Alternatively, partial pyridinium reduction followed by a similar rearrangement may lead to the realisation of this goal by avoiding the enthalpic cost of dearomatisation that is inherent in the possible vinylcyclopropane–cyclopentene rearrangement of 8. Efforts to effect the conversion of 8 to magellaninone are the subject of ongoing studies.

In summary, we report the beneficial effect of a precise amount of a protic additive in the enantioselective Cu-catalysed Diels–Alder reaction using cyclic alkylidene β-ketoesters. This observation has introduced a new stereoinduction model for alkylidene β-ketoester dienophiles, and the development of a stereoselective synthesis of a functionalised

hydrindenone commonly used in the synthesis of complex molecules relevant to natural product synthesis.[2] The utility of the hydrindenone cycloadduct was demonstrated in its application towards the synthesis of magellaninone. Key to the synthetic studies is a robust Stille cross-coupling of a highly congested enol triflate and a unique Meinwald rearrangement/cyclopropanation sequence. These studies should provide the basis for achieving higher levels of enantioselectivity in cycloadditions involving alkylidene β-ketoesters and yield cycloadducts that may be applied in the synthesis of other natural products.

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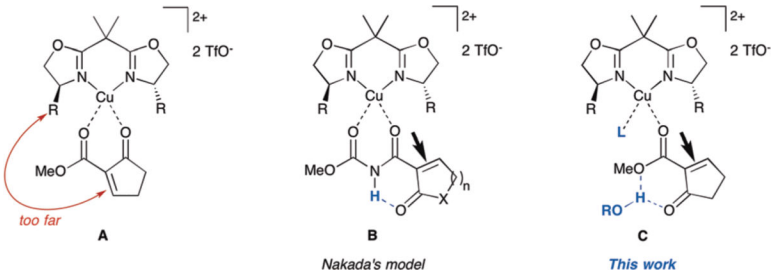
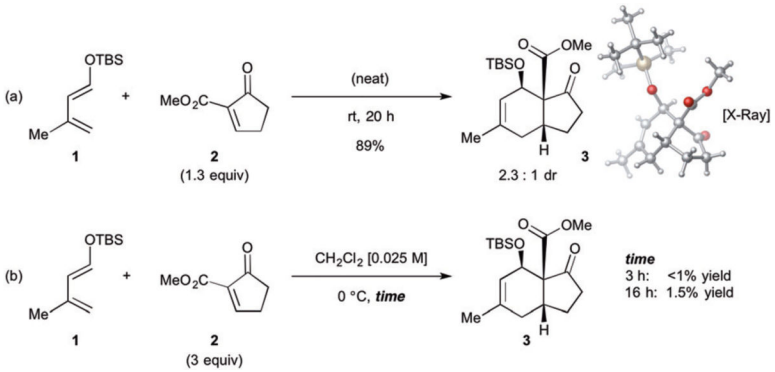


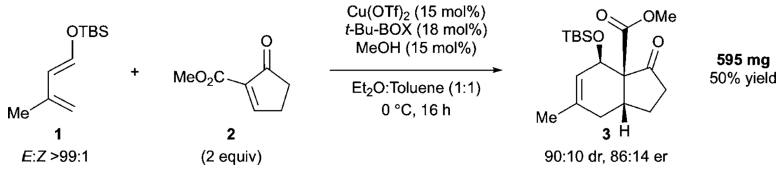
Fig. 1.

Different stereoinduction models for Cu-catalysed enantioselective Diels–Alder using cyclic alkylidene β-ketoesters.



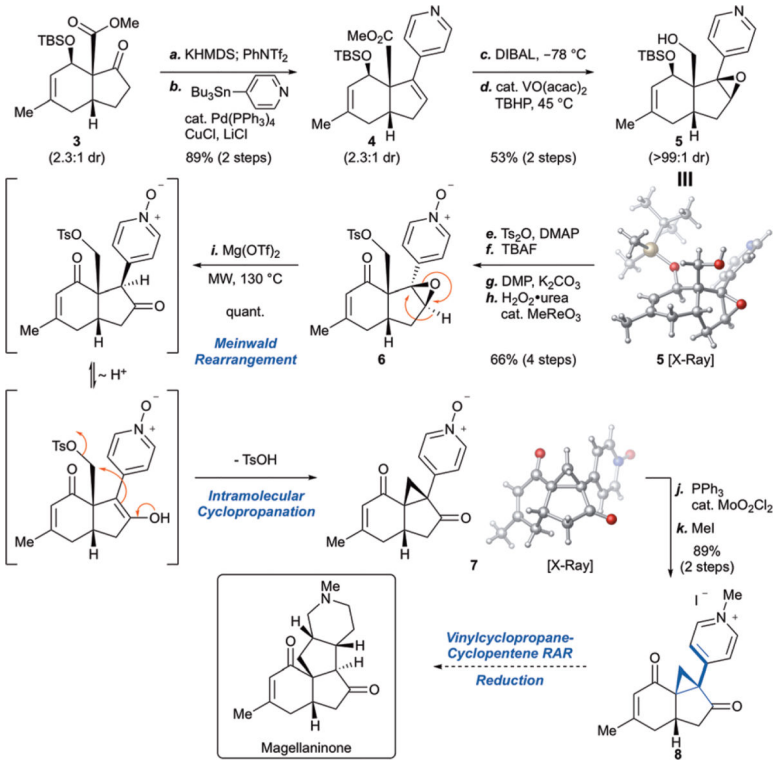
Scheme 1.

Identification of racemic conditions (a) and evaluation of background reaction upon dilution (b).



Scheme 2.

Preparation of hydrindenone **3** on a larger scale.

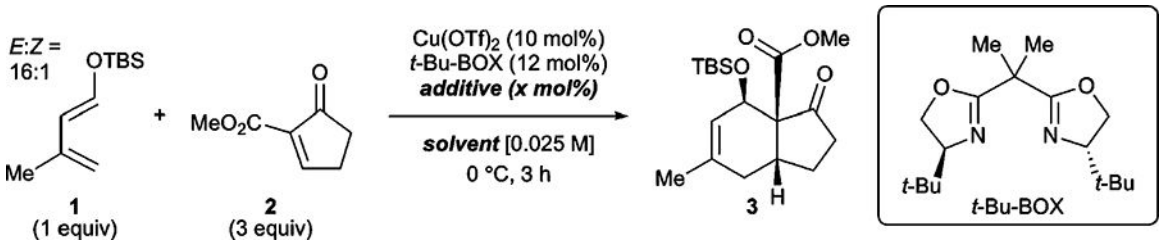


Scheme 3.

Use of hydrindenone **3** as key intermediate towards the synthesis of magellaninone.

Table 1

Effect of solvent and protic additives on the enantioselective Diels–Alder of doubly activated dienophile **2**



Entry	Solvent	Additive (*x* mol%)	Yield[a] (%)	dr[b]	er[c]
1	CH_2Cl_2	—	<5	57:43	51:49
2	CH_2Cl_2	H_2O (10)	51	58:42	51:49
3	EtOAc	H_2O (10)	19	79:21	63:37
4	TBME	H_2O (10)	36	86:14	80:20
5	Et_2O	H_2O (10)	35	87:13	82:18
6	Et_2O	—	<5	66:34	49:51
7[d]	Et_2O	—	39	86:14	79:21
8	Et_2O	H_2O (20)	19	86:14	78:22
9	Et_2O	H_2O (100)	<5	60:40	50:50
10	Et_2O	MeOH (10)	41	88:12	82:18
11[e]	Et_2O:Tol	MeOH (10)	48	89:11	83:17
12[e,f]	**Et_2O:Tol**	**MeOH (10)**	**53**	**90:10**	**86:14**
13[e]	Et_2O:Tol	i-PrOH (10)	44	89:11	83:17

[a] Determined by NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as internal standard.

[b] Diastereomeric ratio determined by NMR analysis of the crude mixture.

[c] Enantiomeric ratio of major diastereomer drawn determined by HPLC using a chiral stationary phase.

[d] $Cu(OTf)_2$ and *t*-BuBOX were stirred in Et_2O at rt for 16 h prior to the reaction (pre-complexation).

[e] Et_2O:toluene ratio = 1:1.

[f] Pure E isomer (*E*:*Z* > 99:1) of diene 1 was used (reaction time: 16 h).