Asymmetric Synthesis of Bicyclic Pyrazolidinones through Alkaloid-Catalyzed [3 + 2]-Cycloadditions of Ketenes and Azomethine Imines

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Abstract: A versatile asymmetric synthesis of bicyclic pyrazolidinones through alkaloid-catalyzed formal [3 + 2]- and [3 + 2 + 2]-cycloadditions of ketenes with azomethine imines is described. The methodology was found to be tolerant of ketene and a variety of monosubstituted ketenes (R = alkyl, OAc). The products were formed in good to excellent yields (71–99% for 24 examples, 39 examples in all), with good to excellent diastereoselectivity in many cases (dr 3 : 1 to 27 : 1 for 22 examples), and with excellent enantioselectivity for most examples (≥ 93% ee for 34 products). In the case of most disubstituted ketenes, the reaction proceeded through a [3 + 2 + 2]-cycloaddition to form structurally interesting bicyclic pyrazolo-oxadiazepinediones with moderate diastereoselectivity (dr up to 3.7 : 1) and as racemic mixtures (3 examples). The method represents the first unambiguous example of an enantioselective reaction between ketenes and a 1,3-dipole.

Introduction

The importance of the bicyclic pyrazolidinone structural motif stems from its presence in many pharmacologically active molecules.[1] These complex molecules exhibit anti-Alzheimer’s activity and related bicyclic pyrazolidinone derivatives have displayed antibiotic, herbicidal, and pesticidal activity (Scheme 1).[1] With this range of biological activity, the development of novel enantioselective methods for the synthesis of bicyclic pyrazolidinones has recently attracted much attention. Despite this activity, catalytic asymmetric entry to bicyclic pyrazolidinones 1 has proven a difficult goal.[2]

A number of approaches to the bicyclic pyrazolidinone structure based on a chiral catalyst-controlled 1,3-dipolar cycloaddition of azomethine imines with various dipolarophile reactant partners have been explored.[3] Fu’s seminal contribution predicated on a Cu(I)/chiral phosphaferrrocene oxazoline-catalyzed [3 + 2]-cycloaddition of azomethine imines with alkynes, to afford the closely related bicyclic pyrazolines, inspired a number of catalytic asymmetric approaches to the pyrazolidinone skeleton.[4–6]

In 2014, Brière and co-workers reported that an unexpected regioisomer of a bicyclic pyrazolidinone 2 could be accessed through the (DHQ)2PHAL-catalyzed Knoevenagel-aza-Michael cyclocondensation reaction of Meldrum’s acid with azomethine imines addition of an azomethine imine with various dipolarophile reactant partners have been explored.[4] Fu’s seminal contribution predicated on a Cu(I)/chiral phosphaferrrocene oxazoline-catalyzed [3 + 2]-cycloaddition of azomethine imines with alkynes, to afford the closely related bicyclic pyrazolines, inspired a number of catalytic asymmetric approaches to the pyrazolidinone skeleton.[5–6]

In 2014, Brière and co-workers reported that an unexpected regioisomer of a bicyclic pyrazolidinone (2) could be accessed through the (DHQ)2PHAL-catalyzed Knoevenagel-aza-Michael cyclocondensation reaction of Meldrum’s acid with azomethine imines.
imines.39 However, only one example was formed in ≥ 90% ee. Additionally, a significant drawback of this method is that it’s limited to Meldrum’s acid as reactant partner for the azomethine imine, effectively eliminating the possibility of substitution α to the carbonyl in the product. In 2015, Studer and co-workers demonstrated that a chiral tetramisole-catalyzed 1,3-dipolar cycloaddition of azomethine imines with mixed anhydrides could provide access to pyrazolidinones 3, containing a tetrahydroisoquinoline moiety, with high enantioselectivity (> 90% ee) for 12 examples.40 However, the tetramisole-catalyzed method is restricted to tetrahydroisoquinoline-containing imines, and as such is unable to provide access to the bicyclic pyrazolidinones represented by 1 or related fused bicyclic 5-membered ring systems. In addition, it is also limited to α-aryl substituents (provided by the anhydride) at the stereogenic center adjacent to the imide carbonyl. The tetramisole-catalyzed reaction was proposed to involve an ammonium enolate intermediate, most likely accessed through deprotonation of an acyl ammonium precursor.41

Also in 2015, Ye and co-workers reported the N-heterocyclic carbene (NHC)-catalyzed reaction of α-chloroaldehydes with azomethine imines to provide bicyclic pyrazolidinones 3, with excellent enantiomeric excess obtained in most cases.42 A related NHC-catalyzed oxidative catalytic [3 + 2] of aldehydes with azomethine imines reported by Ren and co-workers was also found to be successful with moderate to excellent enantioselectivity (66–98% ee) displayed.43

Interestingly, in all of these prior reports of Lewis base-catalyzed enantioselective 1,3-dipolar cycloadditions, ketenes had not been demonstrated to be involved as a reactant partner. For a number of years our group has been focused on reactions, it was found necessary to add propionyl chloride slowly over 10 h to the reaction solution (containing catalyst, azomethine imine, and Hüning’s base) in order to maximize the yield of bicyclic pyrazolidinone 1a, and limit the formation of methylketene homodimer and aldehyde from azomethine imine decomposition.44

In all cases examined, excellent enantioselectivity in the formation of bicyclic pyrazolidinone 1a was observed. However,

Results and Discussion

Reaction optimization

We began our investigation by examining the reaction of in situ-generated methylketene with azomethine imine 4a (where R’ = Ph) in the presence of a variety of cinchona alkaloid derivatives (6–10) in CH₂Cl₂ at −25 °C (Table 1, Figure 1). Phosphine catalysts (PMes₂ and PBU₃) were also examined in preliminary studies but were found to be ineffective (ca. 5% conversion with ethylphenylketene). In the alkaloid-catalyzed reactions, it was found necessary to add propionyl chloride slowly over 10 h to the reaction solution (containing catalyst, azomethine imine, and Hüning’s base) in order to maximize the yield of bicyclic pyrazolidinone 1a, and limit the formation of methylketene homodimer and aldehyde from azomethine imine decomposition.44

We, therefore, turned our attention to the development of a new methodology providing access to bicyclic pyrazolidinones from in situ generated ketenes. In 2016 we reported the first unambiguous catalytic enantiosselective [3 + 2]-cycloaddition of ketenes with azomethine imines.45 In this current article we describe our complete studies on reaction optimization, the scope of the reaction with respect to ketene (unsubstituted, monosubstituted and dissubstituted) and azomethine imine structure (aryl and alkyl substitution), and mechanistic/stereoselectivity analysis.

Table 1. Optimization of alkaloid-catalyzed [3 + 2]-cycloaddition of methylketene with azomethine imine 4a.

| Entry | Cat. | T (°C) | Additive | Yield [%][a] | dr[b] | ee [%][c] |
|-------|------|--------|----------|-------------|------|---------|
| 1     | 6    | −25    | none     | 80          | 1:1  | 98      |
| 2     | 7    | −25    | none     | 63          | 1:1  | 98      |
| 3     | 6    | −78    | none     | (70)        | 1:1  |         |
| 4     | 6    | −25    | LiClO₄   | 0           |      |         |
| 5     | 7    | −25    | Cu(OTf)₂ | (80)        | 1:1  |         |
| 6     | 7    | −25    | Er(OTf)₃ | (73)        | 1:1  |         |
| 7     | 7    | −25    | Yb(OTf)₃ | (70)        | 1:1  |         |
| 8     | 7    | −25    | none     | (40)        | 1.5:1|         |
| 9     | 7    | −25    | none     | (25)        | 2:1  |         |
| 10    | 9    | −25    | none     | 90          | 3:1  | 99      |
| 11    | 9    | −78    | none     | (61)        | 3:1  | 99      |
| 12    | 9    | −25    | Cul     | 89          | 2:1  | 98      |
| 13     | 9    | −25    | none     | 85          | 3:1  | 99      |
| 14     | 9    | −25    | none     | 45          | 3:1  | 94      |

[a] isolated yield for both diastereomers. Conversion as determined by GC-MS in parentheses. [b] dr determined by ¹H NMR or HPLC analysis of crude. (R,S)-isomer = major in most cases. [c] ee determined by chiral HPLC or chiral GC analysis for major diastereomer. [d] 2.5 mol% of catalyst used. [e] 1 mol% of catalyst used.

Figure 1. Catalysts investigated for the [3 + 2]-cycloaddition.
diastereoselectivity was poor-to-modest at first (dr up to 1.5/2:1). A number of Lewis acid additives were tested as a means of enhancing diastereoselectivity, but none provided the desired improvement (entries 4–7, 12). It was only after a switch to the dimeric (DHQ)$_2$PHAL as catalyst, was promising diasteroselectivity (dr 3:1), favoring the trans-diastereomer, achieved (Table 1, entries 10–14).

Catalyst loading (10, 2.5 and 1 mol%) was investigated with a loading of 10 mol% found to be optimal. Only a slight reduction in yield (from 90 % down to 85 %) was obtained at the 2.5 mol% catalyst loading (entry 13), with the same dr and ee obtained as for 10 mol% (entry 10). However, with 1 mol% loading there was a significant deterioration in yield (from 90 % down to 45 %), although dr and ee remained high (dr 3:1, ee 94 %, entry 14). It was decided that the substrate scope of the system should be explored using the 10 mol% catalyst loading, rather than the 2.5 mol% loading, due to the cleaner reactions achieved with the higher loading (background formation of aldehyde from the azomethine imine occurred at low catalyst loadings and in the absence of catalyst).

**Reaction scope**

Initially, the scope of the methodology was investigated with in situ-generated monosubstituted ketenes (34 examples, Table 2). Methyl-, ethyl-, n-propyl-, n-hexyl, and acetoxy-ketene were all found to perform excellently in reaction with aryl-substituted azomethine imines 4, with the desired bicyclic pyrazolidinone 1a–1q being formed with invariably excellent enantioselectivity (34 examples with ee 93–99 % for the major diastereomer). However, the use of in situ-generated phenylketene, chloroketene, thiophenylketene and isopropylketene resulted in formation of no bicyclic pyrazolidinone.

Substitution on the aryl portion of the azomethine imine was flexible, with electron-donating (MeO and Me) and electron-withdrawing (F, Cl) substituents in a variety of positions on the aryl ring being tolerated. Ortho-substitution, however, occasionally led to lower yields (e.g. 1f/ent-1f: 40–45 % and 1p/ent-1p: 26–27 %). Importantly, an alkyl-substituted azomethine imine was found to perform excellently with 1j and ent-1j being formed in 94–95 % ee. However, the reaction was sensitive to the steric bulk of the alkyl substituent, with R$_2$=c-hexyl leading to incomplete conversion and poor diastereoselectivity (dr 1:1, not shown in Table 2).

Diastereoselectivity in pyrazolidinone formation was generally moderate to excellent, with a dr of up to 27:1 being obtained. The trans-diastereomer was formed as the major diastereomer, as determined by X-ray crystallographic analysis of the major isomer of ent-1d.[13] Generally, (DHQ)$_2$PHAL provided higher levels of diastereoselectivity than the pseudoe-nantiomeric (DHQD)$_2$PHAL, for example 1b (dr 5:1) vs. ent-1b (dr 3:1), or 1n (dr 27:1) vs. ent-1n (dr 18:1). Highest diastereoselectivity was observed for ketenes bearing the –OAc substituent, with dr ranging from 12:1 to 27:1 for 6 examples (1m–1q). Examples 1p and ent-1p were notable exceptions giving substantially lower diastereoselectivity, perhaps due to steric interaction with the ortho-methyl aryl group of the azomethine imine. DiastereomERICally pure product could be obtained through a single recrystallization as was demonstrated for ent-1d (dr 3:1), which was recrystallized from CH$_2$Cl$_2$/

**Table 2. Scope of alkaloid-catalyzed [3+2] cycloaddition of monosubstituted ketenes with azomethine imines.**

| Entry | ee | R$_2$ | R’ | ee’ |
|-------|----|-------|----|-----|
| 1a    | 95% | Me    | H  | 95% |
| 1b    | 95% | Et    | H  | 95% |
| 1c    | 95% | n-Pr  | H  | 95% |
| 1d    | 95% | n-C$_6$H$_{13}$ | H | 95% |
| 1e    | 95% | MeO   | H  | 95% |
| 1f    | 95% | Me    | F  | 95% |
| 1g    | 95% | Me    | Cl | 95% |
| 1h    | 95% | Me    | OAc| 95% |

[a] Isolated yield for both diastereomers. (b) dr determined by ‘H NMR or HPLC analysis of crudes. (c) ee determined by chiral HPLC or chiral GC analysis for major diastereomer. (R,S)-isomer is the major isomer from most 9-catalyzed reactions. (S,R)-isomer is the major isomer from most 10-catalyzed reactions.
pentane to provide ent-1d in good yield (67% overall from imine 4d) and with excellent diastereomeric purity (dr 37:1). The reaction was also found to proceed effectively on a 5 mmol scale from azomethine imine 4d, with the desired pyrazolidinone 1d being formed in excellent yield (95%) and with good diastereoselectivity (dr 4:1) favoring the trans-isomer (see Supporting Information Experimental for details).

X-ray crystallographic analysis of ent-1d revealed the absolute configuration, with ent-1d determined to be the (2S,3R)-enantiomer. As formation of ent-1d had been through the (DHQD)PHAL 10-catalyzed reaction, most pyrazolidinone products of the 10-catalyzed reactions were assigned the (2S,3R)-configuration. On the other hand, pyrazolidinone products of the 9-catalyzed reactions were assigned the (2R,3S)-configuration.

We proceeded to explore more difficult cycloadditions such as the reaction of in situ-generated ketene with azomethine imines (Table 3). The difficulty associated with these reactions lies in the high reactivity of ketene, with competing dimerization as a side reaction, and the absence of a ketene substituent being problematic for attaining high levels of enantiocontrol. Ultimately, catalysts 6–9 provided the desired bicyclic pyrazolidinone 1r–1s in moderate to excellent yields but with poor to moderate enantioselectivity (10–43% ee) at room temperature. This demonstrated that the presence of a substituent on the ketene was an essential element for attaining good enantiocontrol in the reaction.

Disubstituted ketenes (methylphenyl-, diphenyl- and dimethyl-) were then examined as substrates for the alkaloid-catalyzed reaction (Table 4). Surprisingly, the product that was favored was the result of a [3 + 2 + 2]-cycloaddition for most disubstituted ketenes rather than the earlier seen [3 + 2]-cycloaddition. The bicyclic pyrazolo-oxadiazepinedione products 11a–11c formed incorporated two molecules of disubstituted ketene, and were formed with good diastereoselectivity favoring the trans (anti)-isomer (dr up to 3.7:1, entries 1 and 2, Table 4), albeit with no optical activity. The lack of enantioselectivity using alkaloid catalysts for reactions of disubstituted ketenes is not surprising given poor results observed by other groups. The relative stereochemistry of 11b was determined to be trans (anti) by X-ray crystal structure analysis. When reactions were run in the absence of the alkaloid catalyst, product 11 was obtained, but as part of a significantly less clean product mixture. Interestingly, when dimethylketene was used as substrate, a product analogous to 11a–11c, incorporating two molecules of dimethylketene, was initially formed, but underwent loss of one molecule of dimethylketene to give the usual bicyclic pyrazolidinone product 1t. We investigated the synthesis of [3,3,0] fused pyrazolidinones (1u/1v) from 11a/11b under a number of reaction conditions (e.g. heating at 40°C for 5 h or directly from 4d, see Supporting Information Experimental) but the desired products were never observed.

**Table 3. Scope of Alkaloid-Catalyzed [3 + 2] cycloaddition of Ketene with Azomethine imines.**

| Entry | Cat. | R1 | Yield [%] | ee [%] | Product |
|-------|------|----|-----------|--------|---------|
| 1     | 6    | Ph | 23        | 43     | 1r      |
| 2     | 7    | Ph | 64        | 32     | ent-1r  |
| 3     | 9    | Ph | 74        | 10     | 1r      |
| 4     | 9    | Ph | 97        | 17     | 1r      |
| 5     | 6    | 4-FC,H4 | 53 | 25  | 1s      |
| 6     | 7    | 4-FC,H4 | 59 | 24  | ent-1s  |

[a] Isolated yield. [b] ee determined by chiral HPLC. [c] Cu (1 equiv.) used as additive.

**Table 4. Scope of alkaloid-catalyzed [3 + 2 + 2] cycloaddition of disubstituted ketenes with azomethine imines.**

| Entry | Cat. | R1 | R2 | Yield [%] | dr [%] | Product |
|-------|------|----|----|-----------|--------|---------|
| 1     | 9    | Ph | Me | 4-MeOC,H4 | 74 | 3.7:1 | 11a      |
| 2     | 9    | Ph | Me | 4-MeOC,H4 | 71 | 3.1:1 | 11b      |
| 3     | 9    | Ph | Me | 4-MeOC,H4 | 29 | 77:3 | 11c      |
| 4     | 9    | Me | Me | 4-MeOC,H4 | 13 | –     | 1t       |
| 5     | 9    | Me | Me | 4-MeOC,H4 | 52 | –     | 1t       |
| 6     | 10   | Me | Me | 4-MeOC,H4 | 55 | –     | 1t       |
| 7     | 10   | Me | Me | 4-MeOC,H4 | 74 | –     | 1t       |

[a] Isolated yield. [b] dr determined by 'H NMR or HPLC analysis of crude. 0% ee for 11a–11c and 1t. [c] Reaction carried out at −78°C. [d] Cu (1 equiv.) added.

**Reaction mechanism**

We propose that bicyclic pyrazolidinones 1 are formed through a stepwise process as shown in Scheme 2. The ketene is formed in situ through dehydrohalogenation of acyl chloride by i-Pr2NET. Alkaloid catalyst ([DHQD]PHAL or (DHQ)2PHAL) adds to the less sterically hindered side of the monosubstituted ketene (or ketene) to form an ammonium enolate (Intermediate I) stereospecifically, favoring the Z-enolate. Intermediate I then adds to the azomethine imine to form zwitterionic Intermediate II with high enantioselectivity and high diastereoselectivity, favoring the trans-isomer. 5-Exo-trig cyclization then leads to the formation of pyrazolidinone 1 with concomitant regeneration of the alkaloid catalyst.

The involvement of a ketene rather than acyl chloride in reaction with the alkaloid catalyst was supported by the following observations/experimental outcomes (Scheme 3). Independent generation of dimethylketene through Zn(0)-mediated dehalogenation of 2-bromopropionyl bromide and its use in the 9-catalyzed reaction with 4d resulted in the formation of 1d, with almost the
same dr (7:1 vs. 6.5:1 for in situ process) and ee (98% ee vs. 99% for in situ process) as for when propionyl chloride and i-Pr$_2$NEt were used (for assumed in situ generation of methylketene, Table 2 conditions). Moreover, the same enantiomer and diastereomer was formed as the major isomer under both sets of reactions conditions, i.e. the same sense of selectivity is observed under both pre-generated ketene and in situ generated ketene reaction conditions. Therefore, we can deduce that ketene is a participant (rather than acyl chloride) in the cycloaddition reactions with azomethine imines.

The possibility of initial addition of the catalyst to the azomethine imine was also explored. An experiment where (DHQ)$_2$PHAL and azomethine imine were dissolved in CD$_2$Cl$_2$ was set up. However, analysis of the reaction mixture by $^1$H NMR spectroscopy revealed no evidence for interaction of (DHQ)$_2$PHAL with azomethine imine, and so most likely initial addition of the catalyst to azomethine imine could be ruled out.

The possibility of background reaction between propionyl chloride/ketene with the azomethine imine was also investigated. It was found that when standard reaction conditions, except for the absence of the alkaloid catalyst 9, were employed for the synthesis of 1d that a complex mixture of products resulted. In addition, when azomethine imine was subjected to reaction with propionyl chloride under standard reaction conditions (−25 °C in CH$_2$Cl$_2$, but with no catalyst and no Hünig’s base), no adduct was formed. This suggested that formation of azomethine imide followed by enolization is unlikely as a reaction pathway for formation of the pyrazolidinone product.

Scheme 2. Proposed reaction mechanism for alkaloid-catalyzed [3 + 2]-cycloaddition.

Scheme 3. Control and mechanistic experiments.

Scheme 4. Proposed reaction mechanism for alkaloid-catalyzed [3 + 2 + 2]-cycloaddition.

Our proposed mechanism for the alkaloid-catalyzed formation of bicyclic pyrazolo-oxadiazepinedione products 11a–11c involves addition of the alkaloid nucleophilic catalyst to the ketene as before, albeit with a lower equilibrium amount of ammonium enolate formed due to lower electrophilicity of the disubstituted ketene (Scheme 4). The ammonium enolate (intermediate I) would then add to the azomethine imine as before to give an intermediate II with moderate diastereoselectivity (dr up to 3.7:1), albeit without any enantioselectivity. However, before cyclization of intermediate II occurs, addition...
of the azomethine imine anionic nitrogen to another molecule of ketene leads to the formation of an enolate (Intermediate III) which adds to the pendant acyl ammonium, leading to the formation of the seven-membered ring (through a formal [3 + 2 +2]-cycloaddition).

Reaction diastereoselectivity rationale

Diastereoselectivity in the [3 + 2]-cycloaddition depends on the steric interactions between substituents (R\(^1\), R\(^2\)) on the azomethine imine and the ketene-derived ammonium enolate (Scheme 5). Gauche approach B of the ammonium enolate to the azomethine imine predicts formation of the trans-diastereomer. However, although it relieves steric interactions between R\(^1\) and R\(^2\), it would suffer from severe steric interactions between \(NR_1\) and R\(^2\). Antiperiplanar approach D of the ammonium enolate to the azomethine imine would also result in the formation of the trans-diastereomer. Analysis of the anti-approach transition state D reveals gauche steric interactions between R\(^1\) and R\(^2\), but no significant interactions between \(NR_1\) and other substituents (in contrast to B and C). Therefore, it is predicted that antiperiplanar approach D is favored.

Best levels of diastereoselectivity (very good to excellent, dr 12 : 1 to 27 : 1 for 6 examples) were generally observed with the -OAc substituent on the ketene (Table 2, 1n–1q). In the latter cases (in contrast to R = alkyl), we surmise that a favorable interaction between lone pairs on the -OAc group and the positively charged nitrogen of the azomethine imine further stabilizes the putative anti approach D leading to a further preference for formation of the trans-isomer (Scheme 5).[14]

To investigate whether the preference for the trans-diastereomer was also influenced by equilibration under the reaction conditions we considered the results of earlier experiments (Scheme 3) and carried out a number of other control experiments. One possibility considered was that Hünig's base-Hünig's base.HCl salt mediated equilibration could be responsible for the high trans-diastereoselectivity observed in some cases. However, comparison of the diastereoselectivity (dr 6.5 : 1) in the synthesis of 1d, where Hünig's base mediated the in situ ketene generation, with the diastereoselectivity (dr 7 : 1) of a reaction carried out in the absence of Hünig's base, i.e. through Zn(0)-mediated dehalogenation of 2-bromopropionyl bromide, showed virtually identical dr values (Scheme 3). This suggested that Hünig's base-Hünig's base.HCl salt does not play an important role in determining diastereoselectivity. The effect of the Zn(II) salt byproduct, ZnBr\(_2\), on dr was also explored. Exposure of ent\(^{-}\)-1e (dr 1.5 : 1) to ZnBr\(_2\) (2 equiv.) in CH\(_2\)Cl\(_2\) at –25°C overnight resulted in only a slight change of dr (to 1.1:1).

We investigated the possibility that the (DHQ)\(_2\)PHAL catalyst could be responsible for equilibration by exposing ent\(^{-}\)-1e (dr 1.5 : 1) to the catalyst 9 at –25°C overnight. However, no significant change (dr 1.2 : 1) in the dr of ent\(^{-}\)-1e was noted. Exposure to silica gel was also briefly investigated as a means of improving the dr of the pyrazolidinones. However, once again no significant change/improvement in dr (dr 1.6 : 1) was noted after stirring of ent\(^{-}\)-1e with silica in CH\(_2\)Cl\(_2\) for 1.5 h at 50–55°C. Finally, treatment of ent\(^{-}\)-1e with KO\(_2\)Bu (dr improved to 3.4 : 1) or DBU (dr improved to 2.4 : 1) led to only moderate improvements in dr. To summarize, there is no evidence that isomerization under the reaction conditions is responsible for the relatively high dr (≥ 6:1) observed in many reactions. Indeed, reagents and reaction conditions (e.g. DBU or KO\(_2\)Bu/50°C) that would usually effect isomerization provided the pyrazolidinone with only moderate diastereoselectivity (dr up to 3.4:1).

Reaction enantioselectivity rationale

Enantioselection is determined in the reaction step involving addition of ketene-derived ammonium enolate (Intermediate I) to azomethine imine to form zwitterionic Intermediate II (Schemes 2 and 6). Approach of the azomethine imine to the si-face of the ammonium enolate, derived from methylketene and (DHQD)\(_2\)PHAL (10), is less sterically hindered than approach to the re-face, where the catalyst –OR substituent (containing the

Scheme 5. Rationale for diastereoselectivity in formal [3 + 2]-cycloaddition (NR\(_1\) = (DHQD)\(_2\)PHAL or (DHQ)\(_2\)PHAL).

Scheme 6. Rationale for enantioselectivity in formal [3 + 2]-cycloaddition (catalyst = (DHQD)\(_2\)PHAL).
phthalazine group) blocks approach. Using the model shown in Scheme 6, the (25,3R)-enantiomer of ent-1a is predicted to be the major enantiomer from the 10-catalyzed reaction, in agreement with the absolute configuration established by X-ray crystallographic analysis for ent-1a.13 The absolute stereochemical outcome is consistent with models previously advanced by the groups of Calter, Lectka and the authors for related alkaloid-catalyzed reactions.10b,11a,17

Conclusion

To conclude, we have developed an alkaloid-catalyzed asymmetric synthesis of bicyclic pyrazolidinones from ketenes and azomethine imines. This represents the first unambiguous enantioselective [3 + 2]-cycloaddition of ketenes with a 1,3-dipole. Bicyclic pyrazolidinones were formed from in situ-generated ketenes and azomethine imines with excellent enantioselectivity in nearly all cases (34 examples ≥ 93% ee). Interestingly, there was a switch to a [3 + 2]-cycloaddition in reactions involving most disubstituted ketenes. Future work will involve applications of the reported methodology and the development of other new nucleophile-catalyzed reactions of ketenes.

Experimental Section

General

THF was freshly distilled from benzophenone ketyl radical under nitrogen prior to use, while Hünig’s base (diisopropylethylamine) was used as received. TMS-quinine, Me-quinidine and dinc dust (1R,2R)-3,5-Dioxo-1-(p-tolyl)tetrahydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl acetate (1 p) was purchased from Aldrich Chemical Co. (DHQ)2PHAL (25 mg, 0.03 mmol) in dichloromethane (2.2 mL) at 25 °C. The reaction was stirred at this temperature for another 6 h and then poured into cold water (15 mL) extracted with dichloromethane (20 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure. The residue was then dissolved in dichloromethane and passed through a plug of regular silica gel (10 g, 2 × 2 cm) using 10% EtOAc/dichloromethane as eluant to afford crude product (free from catalyst) for diastereomeric ratio and enantiomeric excess measurement. Pure product was isolated after further regular silica gel column chromatographic purification using EtOAc/dichloromethane as eluent (mentioned details below).

(25,3R)-2-Methyl-3-phenyltetrahydro-1H,7H-pyrazolo[1,2-a]pyrazole-1,7-dione (ent-1a)

Following general procedure, propionyl chloride (0.053 mL, 0.58 mmol) in dichloromethane (1.0 mL) was added over 10 h to a solution of 4 a (50 mg, 0.29 mmol), Hünig’s base (0.10 mL, 0.58 mmol) and (DHQD)2PHAL (22 mg, 0.03 mmol) in dichloromethane (1.9 mL) at -25 °C. Elution with 3% EtOAc/dichloromethane through silica gel column afforded ent-1a as a light yellowish solid (57 mg, 86%), dr = 1:9.1 (by 1H NMR); HPLC analysis: 97% ee [Daicel Chiral OD-H column; 1.2 mL/min; solvent system: 2% isopropanol in hexane; retention times: 45.1 min (minor), 54.6 min (major)]; Mp: 136–140 °C; IR (thin film) 2984, 2921, 2885, 1770, 1701, 1455, 1319, 1294, 1275, 699 cm⁻¹; 1H NMR (400 MHz, CDCl₃, TMS, Major isomer): δ 7.47-7.33 (m, 5H), 3.57-3.48 (m, 2H), 3.10-2.90 (m, 2H), 2.87-2.74 (m, 2H), 1.19 (d, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl₃, Major isomer): δ 166.7, 160.5, 135.7, 129.2, 129.0, 127.7, 79.2, 52.4, 50.9, 36.6, 11.0; (M+H)⁺ HRMS m/z calcd for (C₁₆H₁₈N₂O₂): 231.1134; found: 231.1131.

General procedure for alkaloid-catalyzed [3 + 2] cycloaddition of ketene and azomethine imine

To a stirring solution of azomethine imine 4 a-4 k (0.30 mmol, 1 equiv.) and catalyst (0.03 mmol. 0.1 equiv.) in dichloromethane (2.0 mL) at -25 °C, Hünig’s base (0.10 mL, 0.60 mmol, 2 equiv.) was added. To this stirring reaction mixture, a solution of acid chloride (0.60 mmol, 2 equiv.) in dichloromethane (1.0 mL) was added over a period of 10 h via syringe pump. The reaction was stirred at this temperature for another 6 h and then poured into cold water (15 mL) extracted with dichloromethane (20 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried over sodium sulfate.
Removal of the solvent under reduced pressure followed by plug of regular silica gel column chromatographic purification using 0.5-2% EtOAc/dichloromethane afforded 11a as a yellow sticky solid (102 mg, 74%), δ:3.7-1 (by 1H NMR; IR (thin film) 2992, 2932, 2837, 1747, 1710, 1525, 1107, 1025, 966 cm⁻¹; 1H NMR (400 MHz, CDCl₃, TMS, Major isomer): δ 7.35-7.21 (m, 4H), 7.21-7.06 (m, 8H), 6.99-6.90 (m, 2H), 4.36 (s, 1H), 3.82 (s, 3H), 3.75-3.64 (m, 3H), 3.26 (t, J = 9.9 Hz, 1H), 2.02 (dd, J = 16.9 & 9.0 Hz, 1H), 1.68 (s, 3H), 1.67–1.56 (m,1H), 1.20 (s, 3H); 13C NMR (100 MHz, CDCl₃, Major isomer): δ 171.7, 171.0, 160.5, 140.2, 136.5, 130.6, 128.9, 128.6, 128.3, 128.0, 127.83, 127.78, 126.8, 126.4, 126.1, 114.9, 72.5, 57.6, 55.5, 47.9, 31.6, 30.1, 18.3; (M+H)+ HRMS m/z calcd for (C₉H₆N₃O₂)⁺: 469.2127; found: 469.2127.

Isomerization experiment

Treatment of crude product (ent-1e) with KOBU
To a solution of ent-1e (23 mg, 0.09 mmol) in THF (37 m) at 0°C, was added KOBU (1 M in hexane, 0.022 mL, 0.25 equiv.) dropwise. The mixture was heated to 50°C and stirred for 30 min. The reaction was quenched with HCl (0.1 M, ~5 mL) added dropwise, and extracted into dichloromethane. The solvent was evaporated to afford the crude product for dr measurement by 1H NMR (dr 3:4:1).

Determination of absolute and relative stereochemistry
For 11a: X-ray crystallographic analysis of ent-1d revealed the relative configuration, was determined to be the (2S,3R)-enantiomer.[11]

For 11b: Relative stereochemistry of 11b was determined to be trans (anti) by X-ray crystallography. Deposition Number 2073137 (for 11b) contains the supplemental crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability Statement
The data that support the findings of this study are available in the supplementary material of this article.

Keywords: azomethine imine · diastereoselectivity · enantioselectivity · ketene · pyrazolidinone

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