Lewis Base Catalysis

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β-Lactones through Catalytic Asymmetric Heterodimerization of Ketenes**

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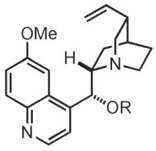
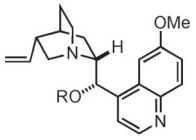
cinchona alkaloids · dimerization · ketenes · organocatalysis · β-lactones

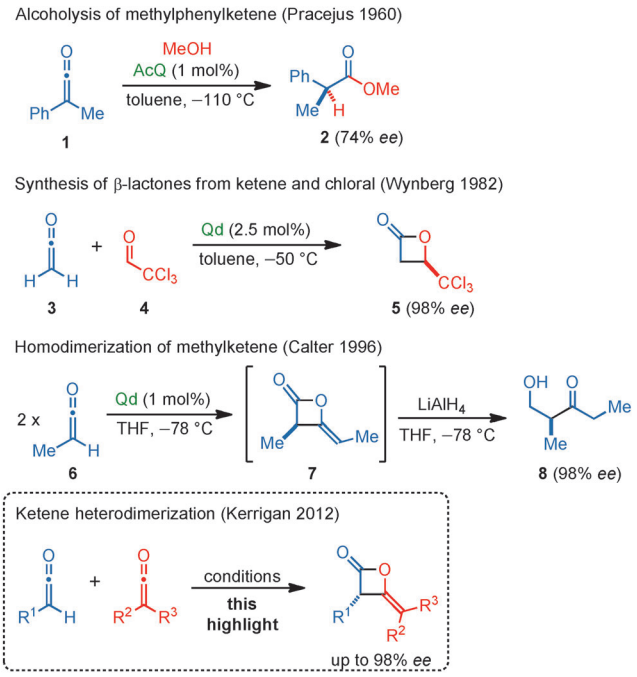
β-Lactones (2-oxetanones) are a privileged structural motif within a multitude of drugs and bioactive natural products.[1] Owing to their strained ring system, they also serve as activity-based probes for chemical biology[2] and as "spring-loaded" intermediates in total synthesis.[3] Consequently, the development of efficient methods for the asymmetric synthesis of β-lactones remains an attractive goal. One important approach involves the dimerization of ketenes under Lewis base catalysis.[4] As early as 1947, Sauer[5] noted that the tertiary amine-mediated dehydrohalogenation of mixtures of acyl chlorides leads to ketene homo- and heterodimers. A kinetic investigation of this reaction and a mechanistic rationale were provided by Pracejus,[6] who also pioneered asymmetric ketene transformations.[7] Treatment of methylphenylketene (**1**) with MeOH in the presence of *O*-acetylated quinine (AcQ)[8] afforded methyl ester **2** in 74% *ee* (Scheme 1). The first catalytic asymmetric synthesis of β-lactones from ketene (**3**) as the donor and chloral (**4**) as the acceptor was reported by Wynberg[9] in 1982 using quinidine (Qd) as chiral Lewis base. The β-lactone **5** was obtained with excellent stereoselectivity and could be converted to malic acid derivatives.



Q R = H (quinine)
AcQ R = Ac
TMSQ R = TMS



Qd R = H (quinidine)
MeQd R = Me



Scheme 1. Short timeline of asymmetric cinchona alkaloid catalyzed transformations of ketenes with focus on β-lactone formations.

Realization of an asymmetric homodimerization of a monosubstituted ketene, such as methylketene (**6**), was hampered by the instability of the corresponding homodimer **7**. In 1996, Calter was able to catalyze the in situ formation of **7** with high enantiomeric excess.[10] Quenching of the reaction mixture with $LiAlH_4$ at low temperature allowed the isolation of hydroxyketone **8**. The utility of this methodology was demonstrated in the synthesis of polypropionate natural products (e.g., siphonarienedione) and fatty acid synthase inhibitors.[11] On the other hand, Romo and co-workers showed that racemic ketene heterodimers constitute useful intermediates for the total synthesis of the proteasome inhibitors (±)-salinosporamide A and (±)-cinnabaramide.[12] While it is possible to gain access to the natural products as single enantiomers through subsequent MPLC separation of diastereomers and recycling steps,[13] this example clearly provides a stimulus for the development of asymmetric heterodimerization methodologies. Very recently, Kerrigan realized an enantioselective cross-dimerization of mono- and

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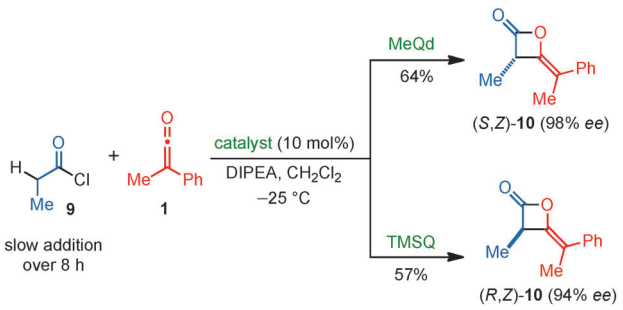
disubstituted ketenes, thus giving rise to a greater variety of chiral β-lactones with excellent enantioselectivities and *E*/*Z* ratios and in good yields.[14]

Apart from a few examples[15] with rather unusual substrates, progress in the cross-dimerization has been hampered by lack of suitable chiral Lewis base catalysts. In a preliminary study[16] by Kerrigan and co-workers, chiral phosphines were found to be too reactive to selectively activate one out of two differently substituted ketenes. At this point, Kerrigan recalled that the trimethylsilyl-protected quinine (TMSQ) catalyst reported by Calter for the homodimerization of monosubstituted ketene is ineffective in methylphenylketene dimerizations. While the attenuated reactivity allows the addition of monosubstituted ketenes (donor) to disubstituted ketenes (acceptor), competing homodimerization had to be inhibited. The situation is somewhat reminiscent of the proline-catalyzed cross-aldolization (see Scheme 4) between nonequivalent aldehydes (and so is the solution to this problem).[17] In order to prevent self-dimerization, the more reactive donor or a suitable precursor has to be added very slowly (syringe pump) to a solution of acceptor and catalyst at a rate that secures proper conversion. Thus, donor accumulation is avoided and the acceptor is kept in excess.

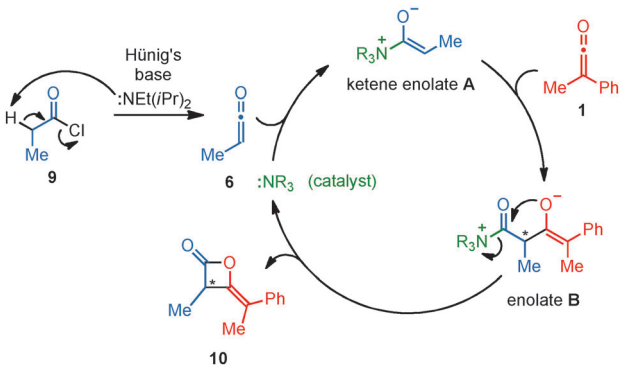
Under optimized reaction conditions, Kerrigan mixed the catalyst (MeQd or TMSQ, 10 mol%) with the relatively unreactive methylphenylketene (**1**) and Hünig's base (diisopropylethylamine, DIPEA) at −25 °C in dichloromethane (0.25 M). Propionyl chloride (**9**) was added to this solution by syringe pump over eight hours in order to generate the more reactive methylketene (**6**) in situ by DIPEA-mediated dehydrohalogenation (Scheme 2). Both enantiomers of the desired heterodimer could be obtained in preparatively useful yields



Scheme 2. Cinchona alkaloid catalyzed heterodimerization of ketenes. DIPEA = diisopropylethylamine.

(57–64%) with excellent *ee* values (94–98%) and *E*/*Z* selectivity (> 97:3 favoring the *Z*-isomer). In contrast to highly unstable homodimer **7**, the aryl substituent renders compound **10** and its analogues sufficiently stable for isolation and characterization. The TMS group exerted a similar product-stabilizing effect. Moreover, mono-TMS-substituted ketenes can be used as designated acceptor ketenes and allow the cross-dimerization of two mono-substituted ketenes.

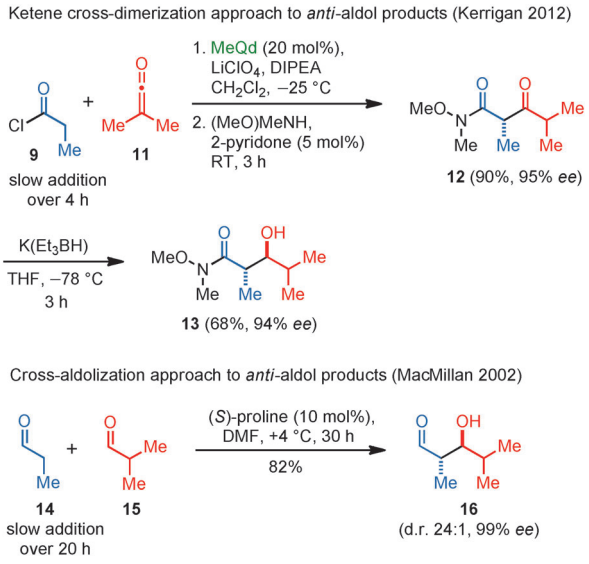
As shown in a mechanistic rationale (Scheme 3), the reaction cycle is initiated by dehydrohalogenation of propionyl chloride (**9**) by the non-nucleophilic Hünig's base. The resulting reactive methylketene (**6**) is activated by addition of



Scheme 3. Proposed mechanism for the one-pot ketene dimerization.

a chiral cinchona alkaloid catalyst to give the nucleophilic ketene enolate **A**. Subsequently, enolate **A** adds to methylphenylketene (**1**). During this step, the stereochemical information is transferred from the catalyst to the newly formed stereocenter (*) in enolate **B**. The catalytic cycle is completed by an intramolecular attack of the enolate oxygen, which forms β-lactone **10** and releases the neutral catalyst. Future in-depth mechanistic studies might help to identify unproductive catalyst resting states or catalyst decomposition pathways in order to reduce the catalyst loading significantly below 10–20 mol% (compared to the historic examples in Scheme 1).

Using their optimized protocol, Kerrigan evaluated the scope of this strategy with different ketene donors and acceptors (17 examples with ≥ 90% *ee*, 40–90% yield). In order to further demonstrate the utility of heterodimeric β-lactones for the synthesis of polyketide-type scaffolds, a short synthesis of synthetically useful Weinreb amide **13** (via the configurationally stable β-ketoamide **12**) was presented (Scheme 4). It is interesting to note that a similar structural motif (**16**) can be generated in the above-men-



Scheme 4. Application of the asymmetric heterodimerization methodology to the synthesis of polyketide scaffolds in comparison with direct aldolizations. DMF = *N*,*N*-dimethylformamide.

tioned cross-aldolization between propionaldehyde **14** and isobutyraldehyde **15**.[17]

In conclusion, 65 years after Sauer's seminal studies on ketene dimerizations, the Kerrigan group has developed the first efficient protocol for asymmetric ketene heterodimerizations. Competing homodimerization of the monosubstituted ketene donor was efficiently suppressed by its slow addition to the disubstituted acceptor. Future research will have to address the cross-dimerization of different monosubstituted alkyl ketenes. Furthermore, a general protocol for the in situ formation of both ketenes—which Kerrigan already demonstrated in a singular example—would greatly enhance the practicality of ketene dimerizations while subsequent catalytic activation of the "spring-loaded" β-lactone moiety might result in new one-pot processes.

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