

Catalytic Asymmetric Heterodimerization of Ketenes

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S Supporting Information

ABSTRACT: In this Communication we describe an unprecedented catalytic asymmetric heterodimerization of ketenes of wide substrate scope. The alkaloid-catalyzed method provides access to ketene heterodimer β -lactones and allows even two different monosubstituted ketenes to be cross-dimerized, with excellent enantioselectivity (17 examples with $\geq 90\%$ ee) and excellent heterodimer regioselectivity observed in all cases.

β -Lactones are interesting targets in synthesis as they are versatile intermediates and are integral structural features of a number of biologically active molecules, such as (–)-panclicin D, orlistat, 1233A, salinosporamide A, and cinnabaramide A.^{1,2} An important route to β -lactones can be achieved via dimerization of ketenes.^{3–5} In 1996 Calter showed that a nucleophilic catalyst system (TMS-quinine or TMS-quinidine) could catalyze the homodimerization of monosubstituted ketenes (aldoketenes) with high enantioselectivity.⁴ In addition, Calter and co-workers have demonstrated that asymmetric alkylketene homodimerization can be applied to the synthesis of polypropionate natural products (siphonarienal, siphonarienedione, and siphonarienolone).⁶ However, the potential of this methodology is compromised due to the requirement for a repeating subunit in the target molecule (i.e., polypropionate) to which the method is applied. On the other hand, ketene heterodimerization (cross-dimerization of two different ketenes) to access ketene heterodimer β -lactones has received little attention, with only a handful of reports dealing with this topic over the last 60 years.^{7–10} A catalytic asymmetric ketene heterodimerization methodology would be expected to provide greater synthetic potential than ketene homodimerization due to the variety of substitution patterns possible within the ketene heterodimer β -lactone structure, and hence there would be opportunities for many applications, beyond polypropionates, in natural product and drug molecule synthesis.

In 1947, Sauer reported that ketene heterodimers could be formed through thermal ketene heterodimerization following an amine-mediated dehydrohalogenation of a mixture of acyl chlorides.⁷ However, the reaction was plagued by very poor yields, low heterodimer regioselectivity, and competing homodimer formation. In the 64 years since then, there have been only three isolated reports of regioselective ketene heterodimerizations, and only two of these described access to β -lactones (rather than to 1,3-cyclobutanediones).^{8–10} These examples involved structurally unusual ketenes such as *tert*-butylcyanoketene or bistrifluoromethylketene and hence their synthetic utility was severely compromised. In view of the complications that have historically beset the ketene hetero-

dimerization reaction, it is not surprising, that no asymmetric heterodimerization reaction has ever been reported. Romo recently demonstrated that racemic ketene heterodimers, obtained using Sauer's method, can be used as intermediates in the synthesis of salinosporamide A and cinnabaramide A.² However, this work is illustrative of the deficiencies of current thermal heterodimerization methodologies. The desired heterodimers were obtained in poor yields (5–12%), with poor regioselectivity and with homodimers being formed as major products of the ketene dimerization. In this Communication, we describe our successful efforts toward the goal of developing a catalytic, regioselective, and enantioselective heterodimerization of ketenes to access ketene heterodimer β -lactones.

During the course of our studies investigating phosphine-catalyzed homodimerizations of ketoketenes (disubstituted ketenes), we became intrigued by the idea of developing an asymmetric entry to ketene heterodimer β -lactones, which seemed to promise greater potential as synthons than the related ketene homodimers.⁵ We anticipated that a stepwise mechanism promoted by a nucleophilic catalytic system would overcome some of the difficulties associated with Sauer's thermal ketene heterodimerization reaction. To that end we began investigations using a variety of catalytic systems that had previously shown success in promoting ketene homodimerizations.^{4,5}

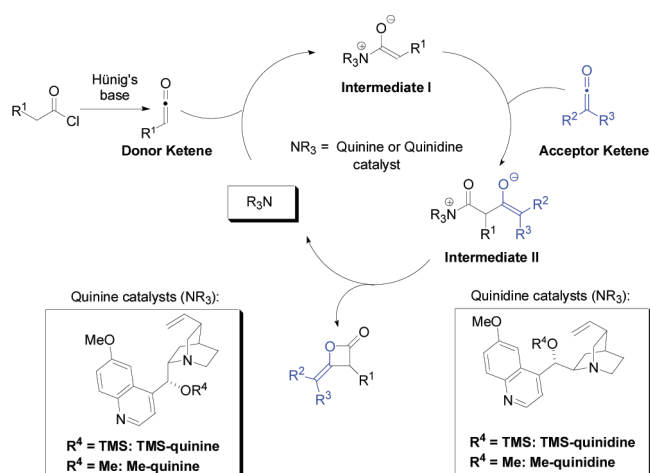
We quickly found that phosphine catalytic systems (BINAPHANE and Josiphos) were too active to facilitate the desired heterodimerization. We next turned our attention to the alkaloid catalytic systems that Calter's group and others had utilized for reactions of monosubstituted ketenes.^{4,11,12} We were encouraged by the observation that TMS-quinine was unable to catalyze the homodimerization of methylphenylketene or dimethylketene.¹³ These results suggested to us a strategy for enabling ketene heterodimerization. The alkaloid catalyst would be mixed with a relatively unreactive ketene (a disubstituted ketene or TMS-ketene, the *acceptor ketene*) and Hünig's base, and a more reactive ketene (generated in situ from an acyl chloride precursor, the *donor ketene*) would be slowly added to the reaction solution (Scheme 1). Addition of the catalyst to the acceptor ketene is expected to be highly reversible, if it occurs at all. Therefore, only one reactive ammonium enolate (derived from the *donor ketene*) would be favorably formed and regioselectivity in ketene heterodimerization would be assured. Moreover, under these reaction conditions, the likelihood of ketene homodimerization occurring would be diminished. Finally, given the strong precedent of asymmetric induction imparted by alkaloid

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Scheme 1. Proposed Mechanism for Alkaloid-Catalyzed Ketene Heterodimerization



catalysis, as observed in Calter's work on ketene homodimerization, we expected that the desired ketene heterodimerization would proceed in a highly enantioselective fashion.^{4a}

We began our optimization of the proposed methodology with methylphenylketene as the less reactive ketene (*acceptor ketene*), and with methylketene (generated from propionyl chloride) as the more reactive ketene (*donor ketene*). All alkaloid catalysts used in this study were easily prepared through one step literature procedures described by the groups of Calter and Gaunt.^{4,14} We found that it was necessary to add propionyl chloride via syringe pump over 8 h to a CH₂Cl₂ solution of methylphenylketene, alkaloid catalyst (Me-quinidine or Me-quinine/TMS-quinine) and Hünig's base, in order to achieve optimal yields of the desired heterodimer (ca. 65%). Complete regioselectivity for the desired heterodimer, as determined by GC-MS and ¹H NMR analysis of the crude product, was observed (Table 1). In addition, the desired heterodimer was obtained as a single olefin isomer (>97:3 favoring the *Z*-isomer).

Next we examined the substrate scope of the methodology exploring a variety of disubstituted ketenes as acceptor ketenes (entries 1–8, Table 2). Both TMS- and Me-protected alkaloid

catalysts provided good to excellent enantioselectivity in ketene heterodimerization, with TMS-quinine (TMSQ) providing access to the (*R*)-enantiomer, and the pseudoenantiomeric Me-quinidine (MeQd) providing access to the (*S*)-enantiomer. Occasionally Me-quinine (MeQ) was used instead of TMS-quinine, if modest conversion in heterodimerization was observed with the latter catalyst (entries 3 and 9, Table 2). Significantly, alkylarylketenes, a dialkylketene, and even diphenylketene were tolerated as the acceptor ketene. In the case of ethylphenylketene (entries 3 and 4, Table 2), lower stereoselectivity for the *Z*-isomer of the olefin was obtained presumably due to the closer steric size of the ethyl and phenyl substituents. Alternatively reversible protonation–deprotonation, by ammonium salt of Hünig's base, of intermediate II may be responsible for the partial isomerization (Scheme 1). For the synthesis of heterodimers **3d** from dimethylketene (entries 7 and 8, Table 2), it was necessary to add 2 equiv of LiClO₄ to limit competing homodimerization of methylketene. Only one heterodimer regioisomer was observed in all cases as determined by GC-MS and ¹H NMR analysis of the crudes. The number of equivalents of acyl chloride used for the synthesis of all examples reported in Table 2 ranged from 0.5 equiv (entry 7 and 8) to 2.0 equiv (entries 1–6). The amount of homodimer formed from the donor ketene ranged from 20 to 40% (of crude mixture) for those cases that required an excess of acyl chloride (entries 1–6) to achieve complete conversion to the desired heterodimer. Those examples that required only 0.5–1.0 equiv of acyl chloride for full conversion to the desired heterodimer afforded <1% donor ketene homodimer (entries 7–10), as determined by GC-MS analysis of the crude products.

We then investigated more challenging cross dimerizations between two monosubstituted ketenes (Table 3). For these heterodimerizations TMS-ketene was selected as the acceptor ketene. We had previously determined that TMS-ketene was unable to undergo homodimerization under alkaloid or even phosphine catalysis conditions. We attributed the failure of homodimerization under these conditions to the low reactivity of onium enolate intermediate I (Scheme 1) derived from TMS ketene, due to the well-known ability of silicon to stabilize α -anions.¹⁵ However we anticipated that TMS-ketene would act

Table 1. Optimization of Alkaloid-Catalyzed Heterodimerization of Ketenes^a

entry	catalyst	addition time of AcCl (h)	solvent	% yield (conv)	% ee ^b
1	TMSQ ^c	1	THF	0	–
2	TMSQ	1	CH ₂ Cl ₂	(40)	nd
3 ^d	MeQ	1	CH ₂ Cl ₂	(50)	nd
4 ^e	MeQ	1	CH ₂ Cl ₂	(65)	nd
5	MeQ	8	CH ₂ Cl ₂	65	83 ^f
6	MeQd	8	CH ₂ Cl ₂	64	98 ^f
7	TMSQ	8	CH ₂ Cl ₂	57	94 ^f

^aOnly one heterodimer regioisomer observed in all cases by GC-MS and ¹H NMR analysis of crude. *Z*:*E* ratio >97:3. ^bee determined by chiral HPLC. ^cTMSQ = TMS-quinine; MeQ = Me-quinine; MeQd = Me-quinidine. ^dentries 1–3: 0.13 M concentration of acceptor ketene in solvent. ^eentries 4–7: 0.25 M concentration of acceptor ketene in solvent. ^fMeQ and TMSQ afforded the (*R*)-enantiomer of **3a**, while MeQd provided the (*S*)-enantiomer of **3a**.

Table 2. Substrate Scope of Heterodimerization of Monosubstituted Ketenes with Disubstituted Ketenes^a

entry	catalyst	R ¹	R ²	R ³	% yield	% ee ^b	Z:E ^c
1	TMSQ	Me	Ph	Me	57	94 (+) ^d	>97:3
2	MeQd	Me	Ph	Me	64	98 (–)	>97:3
3	MeQ	Me	Ph	Et	57	73 (+)	90:10
4	MeQd	Me	Ph	Et	62	98 (–)	84:16
5	TMSQ	Me	Ph	Ph	61	96 (–)	
6	MeQd	Me	Ph	Ph	60	96 (+)	
7 ^{e,f,g}	MeQ	Me	Me	Me	79	91 (+)	
8 ^{e,f,g}	MeQd	Me	Me	Me	90	95 (–)	
9 ^h	MeQ	OAc	Me	Me	52	76 (+)	
10 ^h	MeQd	OAc	Me	Me	57	91 (–)	

^aOnly one heterodimer regioisomer observed in all cases by GC-MS analysis of crudes and NMR analysis of **3**. ^bee determined by chiral HPLC. ^cZ:E ratio determined by ¹H NMR. ^dSign of specific rotation; (+)-enantiomer or (–)-enantiomer. ^eIn these cases 2 equiv of LiClO₄ was used as an additive. ^fIsolated as Weinreb amide derivative due to volatility of heterodimer. ^g20 mol % of catalyst used. ^hIsolated as Weinreb amide due to susceptibility to decomposition on silica gel.

Table 3. Scope of Alkaloid-Catalyzed Heterodimerization of two Monosubstituted Ketenes

entry	catalyst	R ¹	% yield ^a	% ee ^b
1	TMSQ	Me	67	95 (+) ^c
2	MeQd	Me	75	98 (–)
3 ^d	TMSQ	Cl-Et	44	97 (–)
4 ^d	MeQd	Cl-Et	49	98 (+)
5 ^d	TMSQ	<i>n</i> -Hex	53	97 (–)
6 ^d	MeQd	<i>n</i> -Hex	55	95 (+)

^aOnly one heterodimer regioisomer observed in all cases by GC-MS analysis of crudes and NMR analysis of **3**. Z:E ratio >97:3 in all cases. ^bee determined by chiral HPLC or GC. ^cSign of specific rotation; (+)-enantiomer or (–)-enantiomer. ^d20 mol % of catalyst used.

as a suitable acceptor ketene for heterodimerization if it was subjected to reaction with a more reactive ammonium enolate **I**. This proved to be the case as TMS-ketene engaged in asymmetric heterodimerizations with methylketene, *n*-hexylketene and 2-chloroethylketene, with the desired heterodimer being formed with excellent enantioselectivity and complete regioselectivity in each case (Table 3, entries 1–6). The asymmetric entry to heterodimers derived from 2-chloroethylketene (entries 3 and 4), and from *n*-hexylketene (entries 5 and 6) was particularly noteworthy as we anticipated that these examples would function as intermediates for the asymmetric synthesis of salinosporamide **A** and cinnabaramide **A** respectively.² Slightly lower yields (44–49%) were obtained in some cases (entries 3 and 4) due to competing homodimerization of the donor ketene. The amount of donor ketene homodimer formed ranged from 20 to 40% for entries 1–4 (0.5–2.0 equiv of acyl chloride used), while lower levels of donor ketene homodimer (<10%) were observed for entries 5 and 6 (0.5 equiv of acyl chloride used), presumably due to the slower addition of the acyl chloride in the latter cases (12 h for entries 5 and 6 compared to 4–8 h for entries 1–4).

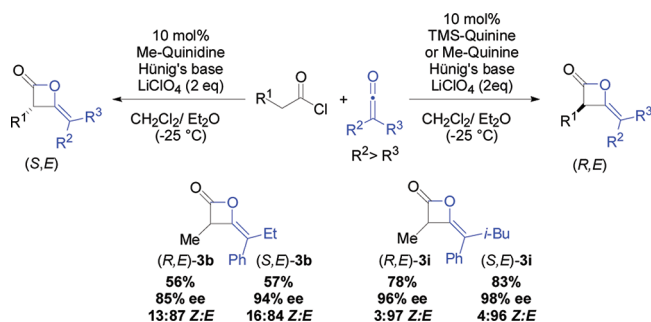
In most cases volatile homodimer was removed under high vacuum or the desired heterodimer was separated from the homodimer by flash column chromatography through a plug of neutral silica (see SI for full details).

We also noted that in certain cases that the olefin geometry of the heterodimer could be switched from *Z* to *E* when LiClO₄ (2 equiv) was added to the alkaloid catalytic system (example **3b** in Scheme 2 compared with entries 3 and 4, Table 2).¹⁶ This ability to switch between olefin isomers of a given heterodimer could be potentially useful for synthetic applications involving aldol reactions of heterodimer-derived enolates.^{6e}

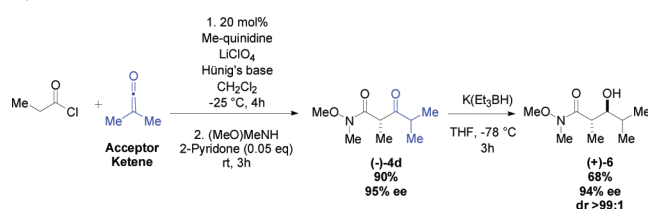
In our initial studies on reactions of the heterodimers, we found that Weinreb amide **4d** derived from heterodimer **3d** underwent diastereoselective reduction when exposed to K₂Et₃BH, to access the synthetically useful β -hydroxyamide **6** with excellent *anti*-diastereoselectivity, and in good yield (Scheme 3).^{6a}

Finally, in situ generation of the acceptor ketene as well as of the donor ketene was investigated (Scheme 4). (–)-**3a** was formed with comparable yield (61%) and with slightly lower enantiomeric excess (91% ee) than when purified methyl-

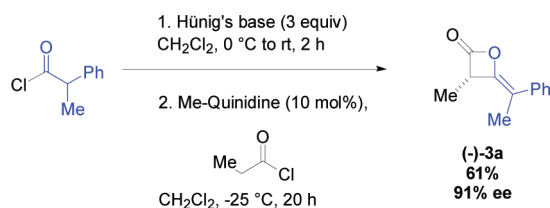
Scheme 2. Isomerization of Ketene Heterodimer Olefin Geometry



Scheme 3. Application of Enantioenriched Ketene Heterodimer to Diastereoselective β -Hydroxyamide Synthesis



Scheme 4. In Situ Generation of Both Ketenes



phenylketene was used (Table 2, entry 2). This result demonstrates the utility of the method and suggests that the scope of the method could be broadened in the future to include less stable non-isolable acceptor ketenes.

In summary, we have developed a catalytic asymmetric heterodimerization of ketenes of wide substrate scope that allows even two different monosubstituted ketenes to be cross-dimerized with excellent enantioselectivity (17 examples with $\geq 90\%$ ee) and excellent regioselectivity (only one heterodimer formed in all cases). Studies are currently underway to apply the new methodology to the asymmetric synthesis of biologically interesting molecules such as cinnabaramide A.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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