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Organocatalytic Dimerization of Ketoketenes

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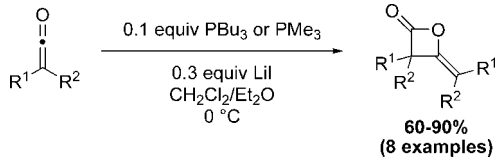


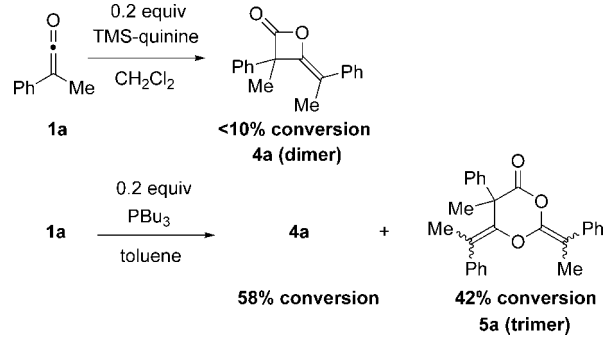
A general method for the catalytic dimerization of ketoketenes is described. Tri-*n*-butylphosphine was found to be the optimal organocatalyst for the racemic reaction. When lithium iodide was used as an additive, the reaction was rendered selective for dimer formation (dimer/trimer ≥16:1). Ring-opening reactions of the ketoketene dimers as well as preliminary studies toward the development of an asymmetric variant are also reported.

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 and 1233A.[1,2] While aldoketene dimer β-lactones have been used extensively in synthetic activities by Calter and co-workers, ketoketene dimers have received less attention due to the paucity of general methods for their preparation.[3−5] Ketoketene dimers are among the most interesting β-lactones from a reactivity standpoint due to the presence of an exocyclic double bond with potential for use as a nucleophile following ring-opening reactions.[6] In addition, β-lactone ketene dimers have recently been shown to have activity as enzyme active site inhibitors by Romo and co-workers.[4]

As part of our program of studies toward the development of new reactions involving phosphonium enolates, we sought to develop an efficient methodology for the dimerization of ketoketenes. We anticipate that the ketoketene dimers may provide access to the quaternary stereogenic center of interesting drug molecules such as the serotonin 1A receptor antagonist LY426965, and (−)-phenserine, a candidate for the treatment of Alzheimer's disease.[7,8] Ketoketene dimers are potential enzyme inhibitors, and such investigations of biological activity are currently in progress at our laboratory.[4]

Some time ago, Elam and, shortly after, Bentrude showed that dimethylketene could be dimerized using trialkyl phosphites as nucleophilic catalysts.[5] However, following these examples of catalytic ketoketene dimerization, no general system and no study of stereoselectivity has emerged in the intervening years. More recently, Calter showed that a nucleophilic catalyst system (TMS-quinine or TMS-quinidine) could catalyze the dimerization of alkyl-substituted aldoketenes with high enantioselectivity.[3]

SCHEME 1. Nucleophile-Catalyzed Dimerization of Methylphenylketene



We initiated a study of methylphenylketene dimerization by investigating the alkaloid catalytic systems previously described by other groups for various [2 + 2]-cycloadditions involving ketenes.[3,9,10] However, only low conversion (<10%) to ketoketene dimer was observed with this class of nucleophilic catalysts (Scheme 1). Inspired by the precedent of Elam's work, we proceeded to investigate tricoordinate phosphorus catalysts for their activity toward methylphenylketene. Tri-*n*-butylphosphine was found to be the most effective of all the catalysts surveyed (Table 1, entry 1). At this point, the reaction afforded a mixture of products including the desired ketoketene dimer product **4a** (58% conversion) as well as ketoketene trimer **5a** (42% conversion). Interestingly, no formation of trimer as a side product had been encountered by Calter's group when they reported the TMS-quinine catalyzed dimerization of methylketene.[3]

The lack of dimer selectivity in the PBu_3 system may be due to the enhanced reactivity of the phosphonium enolate intermediates compared to the ammonium enolate species encountered in TMS-quinine catalyzed reactions.[3] We therefore

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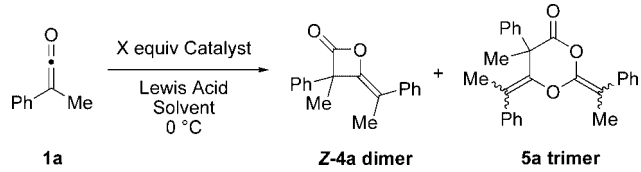
TABLE 1. Effect of Reaction Conditions[a] on Yield and Selectivity of Methylphenylketene Dimerization



1a Z-4a dimer 5a trimer

entry	catalyst (equiv)	LiI (equiv)	solvent	yield[b] (%) (conv, %)	dimer/ trimer[c]
1	PBu_3 (0.2)	0	$PhCH_3$	− (>99)	1.4:1.0
2[d]	PBu_3 (0.2)	0	$PhCH_3$	− (>99)	2.5:1.0
3	PBu_3 (0.2)	0	CH_2Cl_2	− (>99)	4:1
4	PBu_3 (0.2)	1.0	Et_2O	45	>16:1
5	PBu_3 (0.2)	1.0	$PhCH_3/Et_2O$	41	>16:1
6	PBu_3 (0.2)	1.0	THF	50	4:1
7	PBu_3 (0.2)	1.0	CH_2Cl_2 /Et_2O	50	>16:1
8	PBu_3 (0.1)	0.2	CH_2Cl_2 /Et_2O	− (>99)	10:1
9		0.3	CH_2Cl_2/Et_2O	0	
10	PBu_3 (0.1)	0.3	CH_2Cl_2/Et_2O	60	16:1
11	PPh_3(0.1)	0.3	CH_2Cl_2 /Et_2O	47	16:1
12	$P(OEt)_3$ (0.1)	0.3	CH_2Cl_2 /Et_2O	10	
13	TMS-quinine (0.1)	0.3	CH_2Cl_2 /Et_2O	<10	
14[e]	PBu_3 (0.1)	0.3	CH_2Cl_2/Et_2O	78	16:1

[a] Reactions carried out at a concentration of 0.5 M ketoketene in solvent. [b] Isolated yield of *Z*-dimer after flash column chromatography on neutral silica. [c] Determined by ^{1}H NMR analysis of Me signals in the ^{1}H NMR of crude product mixture. [d] Reaction conducted at a concentration of 0.1 M of ketoketene in solvent. [e] Purified by passing through a plug column of neutral silica (iatrobeads).

envisaged that the addition of a Lewis acid to this reaction system would lead to a selective reaction through stabilization of enolate intermediate **3**, which would possess lower reactivity and hence favor dimer formation over trimer formation (Scheme 2).[10−12] Indeed, this change to the protocol proved successful in enhancing dimer formation (Table 1, entries 4, 5, and 7). Subsequent improvements to the methodology involving changing the solvent system to CH_2Cl_2/Et_2O, reducing the catalyst (PBu_3) loading to 0.1 equiv, and reducing the lithium iodide loading to 0.3 equiv led to an improved yield (60%) in the reaction (Table 1, entry 10). Finally, purification by passing the crude product mixture through a plug of neutral silica (iatrobeads), rather than performing standard flash column chromatography, facilitated an improvement to a synthetically useful isolated yield of 78% (Table 1, entry 14).

LiI was found to be the most effective Lewis acid. $LiClO_4$ also proved successful as an additive in modulating dimer selectivity, although a lower yield (44% compared to entry 10, Table 1) of ketoketene dimer was obtained in this case. Other lithium salts, such as LiOTf, and stronger Lewis acids such as $TiCl_4$, $AlCl_3$, and $B(cyclohexyl)_2Cl$ proved less successful leading to poor selectivity or poor conversion/decomposition of starting ketoketene.

The major olefin isomer of methylphenylketene dimer **4a** is presumed to be the *Z*-isomer. This is the isomer that would be expected on the basis of an analysis of the reaction mechanism. A nucleophile would be expected to add to the side of the ketene that is less sterically hindered in order to minimize steric interactions in the transition state leading to **2** and **3** (Scheme 2). Arising from this situation, $A^{1,3}$ strain would also be minimized in product **4**. There is significant

SCHEME 2. Postulated Effect of Lithium Iodide on Product Distribution in PBu_3-Catalyzed Ketoketene Dimerization

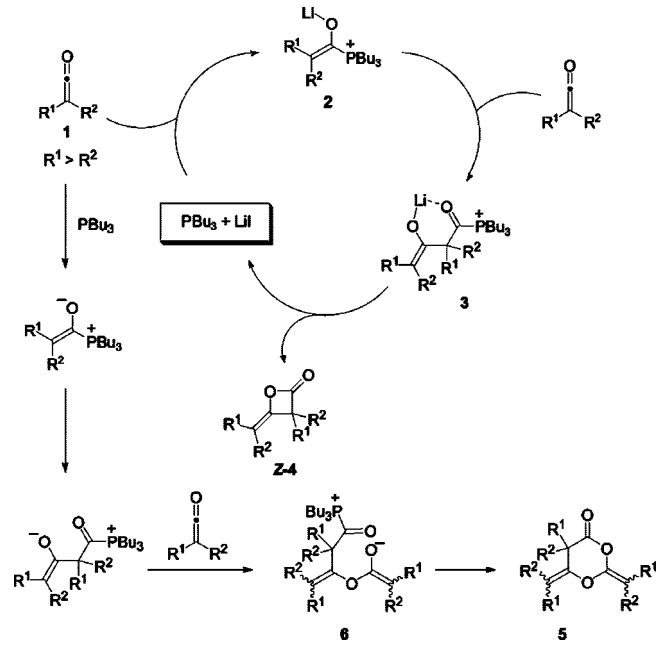
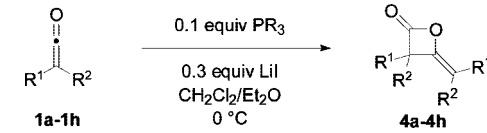


TABLE 2. Yields and Selectivities for the Formation of 4a−h



1a-1h 4a-4h

entry	PR_3	R^1	R^2	yield[a] (%)	*Z*/*E*[b]	product
1	PBu_3	Ph	Me	78	>16:1	**4a**
2	PBu_3	Ph	Et	77	37:1	**4b**
3	PBu_3	4-MePh	Me	90	39:1	**4c**
4	PBu_3	6-MeO-2-naphthyl	Me	62	>16:1	**4d**
5[c]	PMe_3	Ph	Ph	61/78[d]		**4e**
6[c]	PBu_3	Ph	^{i}Bu	84	28:1	**4f**
7	PBu_3	3-thienyl	Et	78	20:1	**4g**
8[c,d]	PMe_3	cyclopentyl	Ph	60	3:1	**4h**

[a] Isolated yield after passing through a plug column of neutral silica (iatrobeads). Purity ≥95% in all cases with the exception of 4 h (90% purity) as determined by GCMS and HPLC analysis. [b] Determined by ^{1}H NMR analysis of Me signals in ^{1}H NMR of crude reaction mixture or by HPLC analysis on an AD column. [c] No LiI was used. [d] 0.2 equiv of PMe_3 was used.

precedence in the work of Tidwell on the addition of organolithiums to ketoketenes and in the work of Calter on the cinchona alkaloid-catalyzed dimerization of aldoketenes to support this analysis.[3,6,13]

Having optimized the conditions for methylphenylketene dimerization, we then examined the substrate tolerance of the methodology. Variation of the alkyl substituent proved successful under the present conditions (entries 2, 6, and 8, Table 2). The methodology also proved to be highly tolerant of variation in the aryl group (entries 3, 4, and 7, Table 2). Sterically demanding substrates (entries 5 and 8, Table 2) were dimerized efficiently when the smaller trimethylphosphine was used instead of tri-*n*-butylphosphine as the dimerization catalyst. The reaction times (see the Supporting Information for full

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details) ranged from 50 min (for formation of **4a**) to 3 days (for formation of **4e**).

The dimerization of cyclopentylphenylketene (**1h**) showed poor selectivity for the *Z*-isomer, presumably because of the similar steric size of the phenyl and the cyclopentyl substituents and the resulting lack of steric bias encountered by the approaching nucleophilic catalyst.

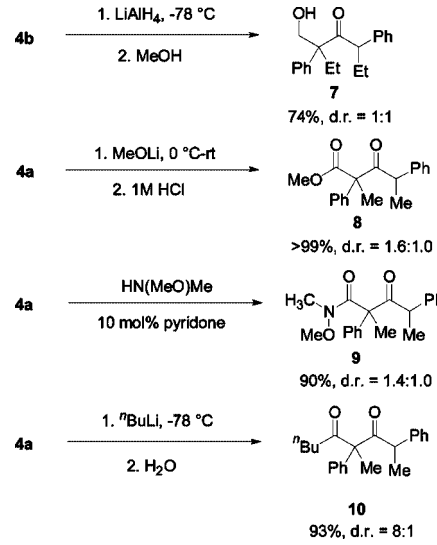
In some cases (entries 5, 6, and 8, Table 2), it was found that a high preference for dimer formation could be obtained even in the absence of lithium iodide. This was ascribed to the lower reactivity of enolate **3e/3f/3h** compared to **3a**. In the case of enolate **3e**, this would be due to electron withdrawal by resonance by two phenyl substituents, while in the cases of **3f** and **3h**, increased steric bulk of the enolate subsitutents (^{i}Bu or Ph vs Me) presumably decreases their reactivity. This would lead to a preference for intramolecular O-enolate ring closure over the trimer forming intermolecular reaction.

We postulate that the ketoketene dimer **4** is formed through the mechanism presented in Scheme 2. Nucleophilic attack of the trialkylphosphine catalyst to the less sterically hindered side of the ketoketene **1** (where R^2 = less sterically demanding substituent) would result in the stereoselective formation of phosphonium enolate **2**.[3,6,13] Nucleophilic addition of **2** to a second molecule of **1** would give rise to a second lithium enolate intermediate **3** stabilized through a 6-membered chelate. 4-*Exo-trig* cyclization and elimination of the phosphine results in generation of the ketoketene dimer product **4**. Some support for this mechanism was provided by ^{31}P NMR spectroscopy. ^{31}P monitoring of the dimerization of **1f** (in the absence of LiI) revealed a strong signal at 34.5 ppm which is a resonance consistent with the structure of lithium-free phosphonium ion **3**.[14] This suggests that **3** is the resting state of the catalyst (for formation of **4f**).

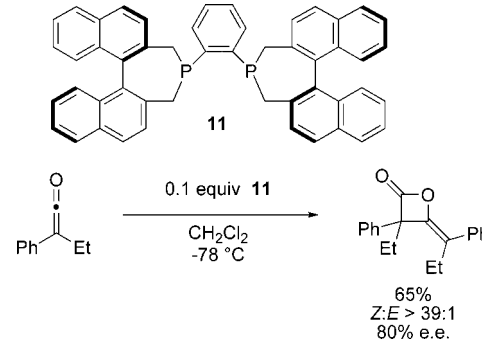
An alternative mechanism would involve attack of the O (rather than C) of phosphonium enolate **2** on a second molecule of ketoketene leading to the formation of a pentacovalent phosphorane species, as was observed by Bentrude and co-workers in the $P(OMe)_3$-catalyzed dimerization of dimethylketene.[5] However, this mechanism was considered less likely due to the absence of any observed ^{31}P signals upfield from external 85% H_3PO_4 (apart from one for PBu_3 at −30.7 ppm).[15] The enhanced stability of enolate intermediates **3** derived from alkylarylketenes relative to those derived from dimethylketene should slow cyclization to a pentacovalent intermediate. In addition, electron-donating alkyl substituents (of PBu_3) on the phosphonium center of **3** would be expected to stabilize the positively charged phosphorus of **3** to a greater degree than when $P(OMe)_3$ is used as a catalyst, hence disfavoring cyclization to a pentacovalent phosphorane intermediate.[14] Taking these factors into account, it is perhaps not surprising that a pentacovalent phosphorane intermediate was not observed in this study.

Having demonstrated the tolerance of the methodology for a variety of ketoketenes, we then investigated the potential utility of the ketoketene dimer products for synthesis by carrying out a variety of ring-opening reactions to access other useful functionality (Scheme 3). β-Lactone **4b** was reduced using $LiAlH_4$ or DIBAL to give the desired β-hydroxyketone **7** in 74% yield as a 1:1 mixture of diastereomers. β-Lactone **4a** was ring opened using MeOLi to afford β-ketoester **8** in an excellent yield of >99% as a 1.6:1.0 mixture of diastereomers. β-Lactone **4a** was also converted to Weinreb amide **9** in good yield (90%, dr = 1.4:1.0) by reaction with the Weinreb amine under conditions developed by Calter and co-workers.[3] Surprisingly, **4a** was converted to 1,3-diketone **10** in high yield (93%) and good diastereoselectivity (8:1) through reaction with excess *n*-BuLi, rather than undergoing double addition to give the expected β-hydroxyketone.[16] The latter reaction underscores the potential of ketoketene dimers to provide exciting opportunities in synthetic activities, highlighting as it does their unusual reactivity.

SCHEME 3. Ring-Opening Reactions of Ketoketene Dimers



SCHEME 4. Asymmetric Variant



Finally, studies toward the development of an asymmetric variant of this reaction have been initiated. We have investigated phosphines possessing axial chirality as these have shown promise in a variety of organocatalytic reactions.[17] Thus far, proof of concept has been demonstrated as ethylphenylketene dimer has been obtained in a good enantiomeric excess of 80% using (*R*,*R*)-BINAPHANE **11** (0.1 equiv) as catalyst (Scheme 4).[18]

Future studies will involve extending the substrate scope of the asymmetric variant of this reaction as well as exploring a number of ring-opening reactions of the ketoketene dimers for applications in drug molecule and natural product synthesis.

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Experimental Section

General Procedure A for Dimerization of Ketoketenes. Ketoketene (1.39 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.4 mL). LiI (0.42 mmol, 0.3 equiv) was dissolved in Et_2O (1.4 mL) and was then transferred to the flask containing the ketoketene solution, and the resulting solution (0.5 M of ketoketene in solvent) was cooled to 0 °C. Tri-*n*-butylphosphine (0.14 mmol, 0.1 equiv) was added in one portion, and the mixture was stirred for the indicated time at the indicated temperature. The reaction was then diluted with CH_2Cl_2 (5 mL) and quenched by adding deionized water (10 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organics were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to provide the crude product for ^{1}H NMR/GCMS analysis. 10% EtOAc/hexane (20 mL) and dichloromethane (5 mL) were added to the crude residue, which was passed through a plug column of neutral silica (iatrobeads, 2 × 2 cm, 10 g) and was eluted with 10% EtOAc/hexane (100 mL). Finally, solvent was removed under reduced pressure to yield the desired ketoketene dimer in high purity (≥95%), in most cases, as determined by GCMS and HPLC analysis, and confirmed by ^{1}H and ^{13}C NMR spectroscopy.

***β*-Lactone 4a (Table 2, Entry 1).** Methylphenylketene (197 mg, 1.48 mmol), stirred for 1 h at 0 °C, was isolated as a colorless oil (152 mg, 78%). The *Z*/*E* ratio was determined to be >16:1 by ^{1}H NMR analysis: IR (thin film) 1881, 1844, 1699, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.52−7.16 (m, 10H), 1.92 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 146.9, 136.2, 135.2, 129.4, 128.6, 128.6, 127.6, 127.4, 126.3, 108.6, 64.4, 19.6, 15.6; MS (EI 70 eV) *m*/*z* 264, 132, 104, 78; (M^+ + Na) HRMS *m*/*z* calcd for $C_{18}H_{16}O_2Na$ 287.1043, found 287.1039.

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Supporting Information Available: Experimental procedures and product characterization data for compounds **4a**−**h** and **7**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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