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Phosphine-catalyzed stereoselective dimerizations of ketenes

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ABSTRACT

Full details of optimisation studies of the phosphine-catalyzed ketene homodimerization reaction and the detailed development of an asymmetric variant are discussed. Studies towards the development of a phosphine-catalyzed ketene heterodimerization reaction are revealed. A discussion of possible reaction mechanisms for the dimerization reactions, supported by spectroscopic analysis of intermediates and trapping experiments, is also presented.

1. Introduction

β-Lactones have historically been important molecules which have seen extensive use as intermediates in the synthesis of complex molecules, and moreover function as integral structural features of many biologically active molecules [1,2]. Important routes to β-lactones include nucleophile catalyzed-[2 + 2] cycloaddition of ketenes with aldehydes, homodimerization of ketenes, and heterodimerization of ketenes [3–6]. The alkaloid-catalyzed enantioselective reaction of methanol with disubstituted ketenes, developed by Pracejus in the 1960s was the first truly high level organocatalytic process [7]. However, in the following years few alkaloid-catalyzed reactions of ketenes were developed, with Wynberg's asymmetric synthesis of β-lactones from ketene and chloro-substituted aldehydes and ketones (e.g. chloral) being the most notable achievement [8]. Over the last two decades, the development of catalytic ketene reactions has exploded, and a number of new classes of catalyst have emerged [9]. The most successful of these new catalyst classes for disubstituted ketenes have been azaferrocenes introduced by Fu's group, N-heterocyclic carbenes reported by the groups of Ye and Smith, and phosphine catalysts introduced by our group [3,9]. Recently, we determined that phosphines (trialkyl- and dialkyaryl-) were excellent catalysts for promoting a range of formal [2 + 2] cycloadditions of ketenes, including with aldehydes to give highly substituted *trans*-β-lactones, with N-tosylimines to give *trans*-β-lactams, and catalytic homodimerization of disubstituted ketenes to provide access to ketene homodimer β-lactones [3,10,11]. We have noted that phosphines often provide superior substrate scope compared to N-heterocyclic carbenes and azaferrocene catalysts, especially for difficult substrate classes, such as chiral aldehydes [12]. Furthermore, they often provide complementary access to a given isomer of product, e.g. the *trans*-isomer of β-lactam from N-tosylimines, relative to the *cis*-isomer provided by azaferrocene catalysis [10].

In the 1960s, Elam and, shortly after, Bentrude showed that the homodimerization of dimethylketene could be promoted by trialkylphosphite nucleophilic catalysts [4b-4d]. In 1996, and more comprehensively in 2003, Calter showed that a nucleophilic catalyst (TMS-quinine or TMS-quinidine) could catalyze the homodimerization of a number of in situ-generated alkyl substituted aldoketenes with high enantioselectivity [5]. Ketene dimer β-lactones have been used extensively in the synthesis of polypropionate natural products by Calter and co-workers, and by Romo's group in the synthesis of fatty acid synthase inhibitors and tetronic acids [5,13]. In 2009 our group reported that a trialkylphosphine catalyst could provide a versatile system for

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promoting the homodimerization of disubstituted ketenes [11]. We also demonstrated that Binaphane and, later, Josiphos were excellent chiral catalysts for promoting the enantioselective homodimerization of disubstituted ketenes [11]. Around the same time Ye's group published their work on the N-heterocyclic carbene-catalyzed asymmetric ketene homodimerization reaction [14]. However the latter method was found to be unsuitable for the homodimerization of *ortho*-substituted alkylarylketenes and dialkylketenes, whereas the Josiphos system worked well for those substrates, in addition to the more commonly explored alkylarylketenes (methylphenylketene, ethylphenylketene, etc.) [11c]. In this paper, we discuss the extensive optimisation involved in the development of the phosphine-catalyzed enantioselective homodimerization process, the scope and limitations of the phosphine-catalyzed homodimerizations (both non-enantioselective and enantioselective variants), phosphine-catalyzed ketene heterodimerization, in situ ketene generation studies, and mechanistic studies of the phosphine-catalyzed dimerization reactions.

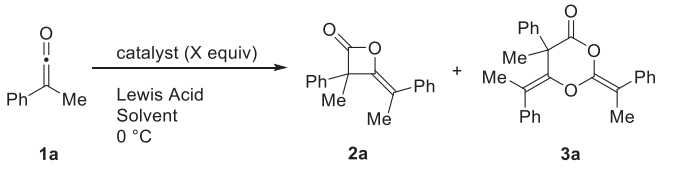
2. Results and discussion

2.1. Optimisation of the phosphine-catalyzed homodimerization reaction (non-enantioselective variant)

Optimisation of the catalytic homodimerization of disubstituted ketenes initially revolved around methylphenylketene as the test substrate (Table 1). A number of nucleophilic catalysts were investigated for their ability to promote the desired homodimerization in forming ketene homodimer β-lactone **2a**. Interestingly alkaloid catalysts were found to be ineffective with only *ca.* 5–10% conversion to homodimer being observed (e.g. Table 1, entry 1). Phosphites, such as triethylphosphite, were also found to perform poorly (e.g. entry 2). On the other hand, the trialkylphosphine, tri-*n*-butylphosphine, was found to be an excellent catalyst for promoting the desired homodimerization reaction (entries 3–5). Methylphenylketene homodimer **2a** was formed, along with trimer **3a**, with complete conversion of ketene to product when 20 mol% of the tri-*n*-butylphosphine catalyst was employed. Careful optimisation revealed that LiI as an additive effectively suppressed trimer formation (entry 6). We propose that the main effect of the LiI additive is to stabilize enolate intermediate **2aa** favouring cyclisation to dimer rather than further reaction with ketene to give trimer (Scheme 1).

Other Lewis acids were evaluated, e.g. $LiClO_4$, LiOTf, $TiCl_4$, $AlCl_3$, and B(*c*-Hex)$_2$Cl, but all afforded lower yield of homodimer **2a** than when LiI was employed. The amount of lithium iodide used was reduced to 0.3 equiv without any significant increase in trimer formation and importantly with an increase in the yield of homodimer being observed (entry 12). At the same time the tri-*n*-butylphosphine catalyst loading was dropped to 10 mol% (0.1 equiv) without loss of reaction efficiency. Ultimately the best isolated yield for **2a** of 82% was obtained after purification through a plug column of neutral silica, rather than through a standard sized column (entry 14). By way of comparison, triphenylphosphine was found to perform moderately well (47%) under identical reaction conditions (entry 13), but clearly the superior nucleophilicity of the trialkylphosphine catalyst is needed for optimal ketene homodimerization.

Table 1
Effect of reaction conditions[a] on yield and selectivity of methylphenylketene homodimerization.

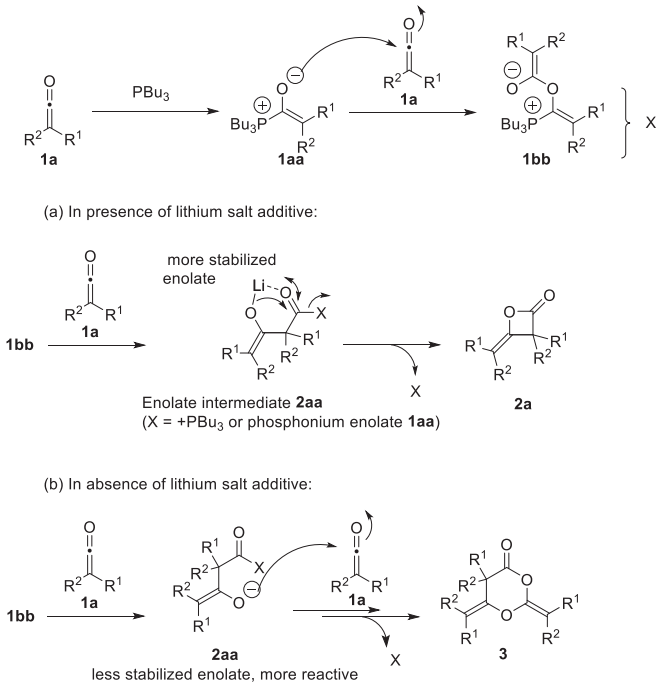


Entry	Catalyst (Equiv)	LiI Equiv	Solvent	Yield[b] (Conv)	2a: 3a[c]
1	TMS-quinine (0.1)	0.3	CH_2Cl_2/Et_2O	<10	–
2	$P(OEt)_3$ (0.1)	0.3	CH_2Cl_2/Et_2O	10	–
3	PBu_3 (0.2)	0	$PhCH_3$	- (>99)	1.4:1
4[d]	PBu_3 (0.2)	0	$PhCH_3$	- (>99)	2.5:1
5	PBu_3 (0.2)	0	CH_2Cl_2	- (>99)	4:1
6	PBu_3 (0.2)	1.0	Et_2O	45	>16:1
7	PBu_3 (0.2)	1.0	$PhCH_3/Et_2O$	41	>16:1
8	PBu_3 (0.2)	1.0	THF	50	4:1
9	PBu_3 (0.2)	1.0	CH_2Cl_2/Et_2O	50	>16:1
10	PBu_3 (0.1)	0.2	CH_2Cl_2/Et_2O	- (>99)	10:1
11	–	0.3	CH_2Cl_2/Et_2O	0	–
12	PBu_3 (0.1)	0.3	CH_2Cl_2/Et_2O	60	16:1
13	PPh_3 (0.1)	0.3	CH_2Cl_2/Et_2O	47	16:1
14[e]	PBu_3 (0.1)	0.3	CH_2Cl_2/Et_2O	82	16:1

[a] Reactions carried out at [0.5 M] of 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 ^{1}H NMR of crude product mixture.
[d] Reaction conducted at [0.1 M] of ketoketene in solvent.
[e] Purified by passing through a plug column of neutral silica (iatrobeads).

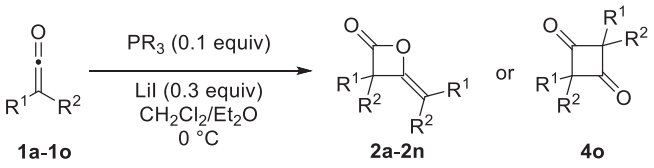
2.2. Substrate scope

We then proceeded to evaluate the scope of the tri-*n*-butylphosphine-catalyzed ketene homodimerization (Table 2). In many cases (for $R^2 \neq$ Me) it was not necessary to use lithium iodide as an additive in order to minimise trimer formation. This was due to the lower reactivity of enolate intermediates **2aa** in some cases (because of resonance stabilisation, e.g. $R^1 = R^2 =$ Ph for entries 6 and 7, or steric bulk of R^2 alkyl substituent e.g. for $R^2 =$ Et, *n*-Bu, *i*-Bu), compared to those derived from methylphenylketene ($R^2 =$ Me).



Scheme 1. Role of lithium salt additive in ketene homodimerization and trimer formation.

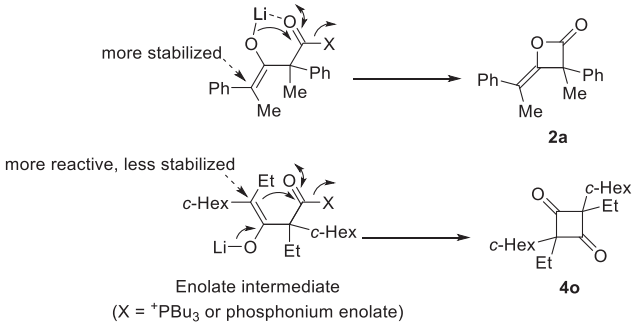
Table 2
Yields and diastereoselectivities for the formation of 2a-4o.



Entry	PR_3	R^1	R^2	Yield[a]	Z:E[b]	Product
1	PBu_3	Ph	Me	82	>16:1	**2a**
2	PBu_3	Ph	Et	84/98[c]	37:1	**2b**
3[c]	PBu_3	Ph	*n*-Bu	99	nd	**2c**
4[c]	PBu_3	Ph	*i*-Bu	84	28:1	**2d**
5[c]	PBu_3	Ph	Bn	(64)[d]	nd	**2e**
6[c]	PBu_3	Ph	Ph	67	–	**2f**
7[c]	PMe_3	Ph	Ph	61/78[e]	–	**2f**
8[c]	PBu_3	2-ClC_6H_4	Me	99	nd	**2g**
9[c]	PBu_3	2-tolyl	Me	97	nd	**2h**
10	PBu_3	4-tolyl	Me	90	39:1	**2i**
11[c]	PBu_3	4-tolyl	Et	99	nd	**2j**
12	PBu_3	6-MeO-2-Naphthyl	Me	62	>16:1	**2k**
13	PBu_3	3-Thienyl	Et	78	20:1	**2l**
14[c,f]	PBu_3	Me	Me	73 (94)[g]	–	**2m**
15[c,e]	PMe_3	*c*-Pentyl	Ph	60	3:1	**2n**
16[h]	PBu_3	*c*-Hexyl	Et	87	–	**4o**

[a] Isolated yield after passing through a plug column of neutral silica (iatrobeads). Purity ≥95% in all cases with the exception of **2n** (90% purity) as determined by GCMS and HPLC analysis.
[b] Determined by ^1H NMR analysis of Me signals in ^1H NMR of crude reaction mixture or by HPLC analysis on an AD column.
[c] No LiI was used.
[d] Conversion as determined by GC-MS analysis.
[e] 0.2 equivalents of PMe_3 was used.
[f] Reaction carried out in THF at −25 °C.
[g] Isolated yield for β-ketoalcohol derivative.
[h] 1,3-Cyclobutanedione regioisomer.

As a result, a preference for intramolecular O-enolate ring closure to give dimer rather than trimer-forming reaction of **2aa** was observed (Scheme 1). Variation of the alkyl substituent was tolerated with high yields obtained for R^1 = Me, Et, *n*-Bu and *i*-Bu (entries 1–4). Although lower efficiency was noted for R^2 = Bn (entry 5), the very stable ketene, diphenylketene, could be subjected to homodimerization, albeit with longer reaction times involved (up to 3 days for entry 7). It was notable that *ortho*-substituted aromatics for R^1 could be accommodated (entries 8 and 9) as well as heteroaromatic substituents (e.g. thiophene, entry 13), without any loss of reaction efficiency. Dialkylketenes such as dimethylketene and ethyl-*c*-hexylketene also performed well under the optimised conditions. Interestingly, homodimerization of ethyl-*c*-hexylketene led to the formation of a 1,3-cyclobutanedione



Scheme 2. Regioselectivity in phosphine-catalyzed ketene homodimerization.

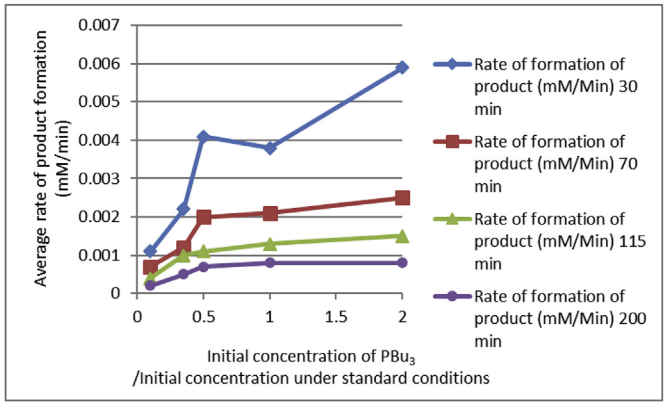


Fig. 1. Catalytic homodimerization of isobutylphenylketene at different concentrations of PBu_3. Standard conditions refers to a starting concentration of 0.1 M for isobutylphenylketene in CH_2Cl_2 and 0.01 M (0.1 equiv.) for PBu_3 in CH_2Cl_2.

regioisomer, rather than the β-lactone regioisomer, as the major product. We attribute that result to a change in the electronics arising from dialkyl-substitution, causing the putative enolate intermediate to react through the C-atom rather than through the O-atom (Scheme 2). When a phenyl substituent is present, electron delocalization, by resonance, can help to stabilize the enolate intermediate, rendering the C end of the enolate less reactive, with the enolate displaying a tendency to react through the O-atom (which is also a less sterically hindered nucleophilic site). However, when dialkyl-substitution is present at the α-position of the enolate, no such electron delocalization at the C-atom end of the enolate is possible, and so the enolate displays a preference for reacting through the C-atom of the enolate to give the 1,3-cyclobutanedione regioisomer.

2.3. Kinetics studies

In order to measure the rate of product formed per unit time with differing reaction conditions, kinetic experiments were carried out by subjecting isobutylphenylketene to homodimerization catalyzed by tri-*n*-butylphosphine. These reactions were carried out by varying the concentration of the catalyst and concentration of ketene in different experiments. The rate of **2d** formation was monitored by GC-MS every 30, 70, 115 and 200 min. Fig. 1 shows the results for the formation of ketene homodimer **2d** at various concentrations of tri-*n*-butylphosphine (0.01–0.2 equiv) with constant

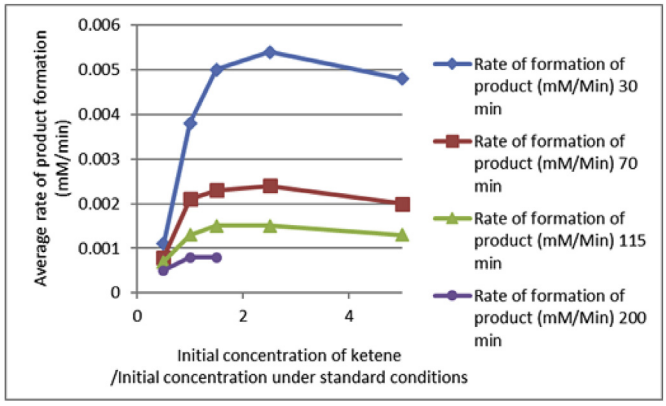
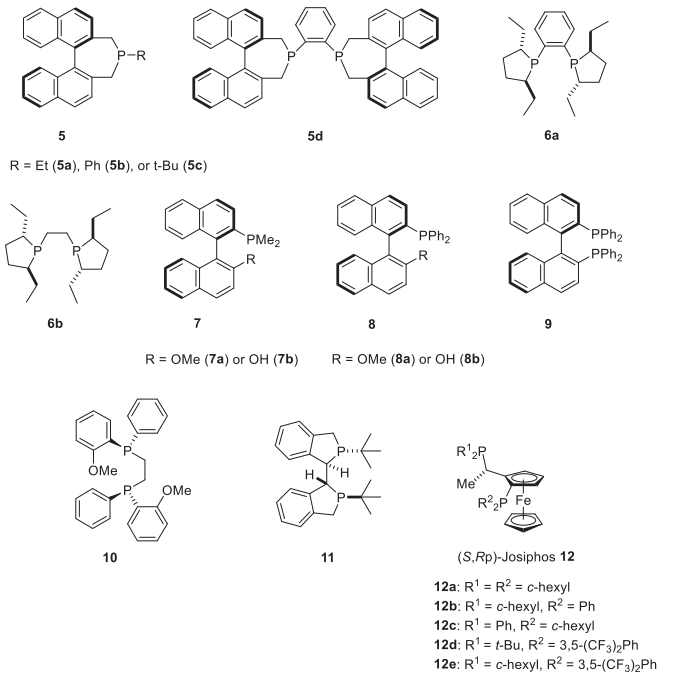


Fig. 2. Catalytic homodimerization of isobutylphenylketene at different concentrations of ketene, with constant equivalents of PBu_3 (0.1 equiv) in CH_2Cl_2.

Table 3
Catalyst screening for catalytic asymmetric homodimerization of methylphenylketene.



Entry	Phosphine	Conc (M)	2a:3a[a]	% Conv (% Yield)[b,c]	% ee[d]
1	**5a**	0.5	nd	(30)	9
2	**5b**	0.5	nd	(15)	14
3	**5c**	0.5	nd	(20)	26
4	**5d**	0.5	nd	(70)	26
5[e]	**5d**	0.5	nd	(78)	33
6	**6a**	0.5	nd	30	4
7	**6b**	0.5	nd	(63)	0
8	**7a**	0.5	nd	(60)	9
9[f]	**7a**	0.5	nd	nd	10
10	**7b**	0.5	nd	<5	0
11	**8a**	0.5	nd	20	8
12	**8b**	0.5	nd	3	0
13	**9**	0.5	nd	nd	0
14	**10**	0.5	nd	30	9
15	**11**	0.5	nd	10	13
16[g]	**12a**	0.5	4:1	>99	73
17[e]	**12a**	0.5	nd	12	64
18[h]	**12a**	0.5	2.1:1	>99	80
19	**12b**	0.5	2.3:1	>99	78
20	**12c**	0.5	1.8:1	>99	2
21	**12d**	0.5	–	0	–
22	**12e**	0.5	2.3:1	>99	82
23	**12e**	0.25	5:1	>99	nd
24	**12e**	0.125	32:1	>99	80
25[i]	**12e**	0.125	32:1	>99 (74)	90

[a] Dimer:trimer ratio determined by ^{1}H NMR or GC-MS analysis of crude product.
[b] % Yield is isolated yield for **2a**.
[c] *Z*:*E* > 32:1 in most cases as determined by GC-MS analysis, and a comparison of spectroscopic data with that of ref 14.
[d] % ee of dimer determined by chiral HPLC analysis.
[e] Reaction conducted at −78 °C.
[f] Conducted in the presence of 0.3 equiv LiI.
[g] Reaction conducted at 0 °C.
[h] Reactions in entries 18–25 conducted at −25 °C.
[i] Catalyst solution was also cooled to −25 °C.

initial concentration of isobutylphenylketene (0.1 M) in CH_2Cl_2. Fig. 1 shows that the rate of **2d** formation increases with the increase in concentration of the catalyst (PBu_3), with 0.2 equiv (0.02 M) of PBu_3 being optimal (initial concentration of PBu_3/initial concentration under standard conditions = 2, Fig. 1).

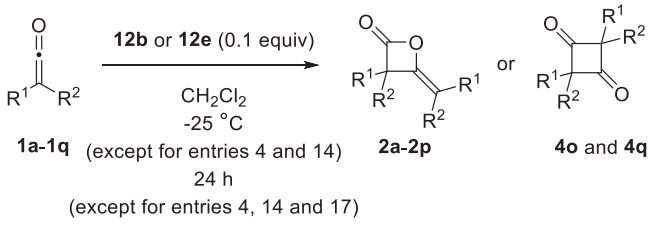
Fig. 2 indicates the rate of product formed at different concentrations of ketene in CH_2Cl_2 while at constant equivalents of PBu_3 (0.1 equiv). The optimal concentration of ketene for best reaction rate was found to be 0.25 M (initial concentration of ketene/initial concentration under standard conditions = 2.5, Fig. 2).

The kinetic data showed that the rate of the homodimerization reaction was dependent upon the catalyst concentration with 0.2 equiv (0.02 M) being optimal, although 0.1 equiv (0.01 M) and even 0.05 equiv (0.005 M) of PBu_3 also worked effectively. The rate of the reaction was also found to be dependent upon the concentration of the ketene with 0.25 M proving optimal, although 0.15 M and 0.5 M also gave good results in terms of rate.

2.4. Optimisation of the phosphine-catalyzed enantioselective homodimerization reaction

Having identified tri-*n*-butylphosphine as the optimal nucleophilic catalyst, we then proceeded to investigate a range of chiral phosphines in order to identify a catalyst for enantioselective ketene homodimerization. We were initially attracted to phosphines exhibiting atropisomerism, such as phosphepines, MOP

Table 4
Scope of Josiphos-catalyzed asymmetric homodimerization of ketoketenes.



Entry	R^1	R^2	Product	% Yield[a]	% ee[b]	Config
1[c]	Ph	Me	(−)-**2a**	65	94	*S*
2[d]	Ph	Me	(+)-**2a**	74	90	*R*
3[e]	Ph	Et	(−)-**2b**	93	86	*S*
4[f]	Ph	Et	(−)-**2b**	65	80	*S*
5[g]	Ph	Et	(+)-**2b**	86	90	*R*
6[e]	Ph	Bn	-	(10)[h]	nd	-
7[g]	Ph	*n*-Bu	(+)-**2c**	90	89	*R*
8	Ph	*i*-Bu	-	0	–	-
9[c]	2-ClC_6H_4	Me	(+)-**2g**	45	96	*S*
10[d]	2-tolyl	Me	(+)-**2h**	80	94	*R*
11[e]	4-ClC_6H_4	Et	(−)-**2p**	81	94	*S*
12[e]	4-tolyl	Et	(−)-**2j**	99	85	*S*
13[e]	3-thienyl	Et	(−)-**2l**	68	46	*S*
14[f]	3-thienyl	Et	(−)-**2l**	61	78	*S*
15[d]	*c*-hexyl	Me	**4q**	97[i]	na	
16[e]	*c*-hexyl	Et	**4o**	77[i]	na	
17[d]	Me	Me	**2m**	75	na	

[a] Isolated yield (%). Dimer:trimer ≥32:1 in all cases. *Z*:*E* > 32:1 as determined by GC-MS analysis, and a comparison of spectroscopic data with that of ref 14.
[b] % ee determined by chiral HPLC analysis.
[c] (S,R_p)-**12e** was used as catalyst (Method C).
[d] (R,S_p)-**12e** was used as catalyst (Method C).
[e] (S,R_p)-**12b** was used as catalyst (Method D).
[f] (*R*)-Binaphane was used as catalyst and reaction conducted at −78 °C for 48 h (Method E).
[g] (R,S_p)-**12b** was used as catalyst (Method D).
[h] Conversion as determined by GC-MS analysis.
[i] Obtained as a mixture of *cis*- and *trans*-isomers.

derivatives, and BINAP. Phosphepines, in particular, were considered to be promising catalysts due to their track record of success in reactions involving allenoates, as demonstrated by Fu's group [15]. Once again methylphenylketene was utilized as the standard test substrate.

Monophosphepines such as **5a**-**5d** were found to give modest enantioselectivity (up to 33% ee, Table 3, entries 1–5). Interestingly (*R*)-Binaphane **5d** was found to be a good enantioselective catalyst for the homodimerization of ethylphenylketene (80% ee), but it proved to be less successful with methylphenylketene as a substrate (entries 4 and 5) [11a,11c]. As many complex molecule targets of interest (e.g. LY426965) possess a methyl group at a quaternary stereocenter, we were motivated to develop a more successful method for the enantioselective homodimerization of methylphenylketene [16]. We next turned our attention to chiral phosphines possessing planar chirality [17]. Commercially available Josiphos derivatives **12a**-**12e** were examined for reactivity and enantioselectivity in the homodimerization of methylphenylketene (entries 16–25) [18].

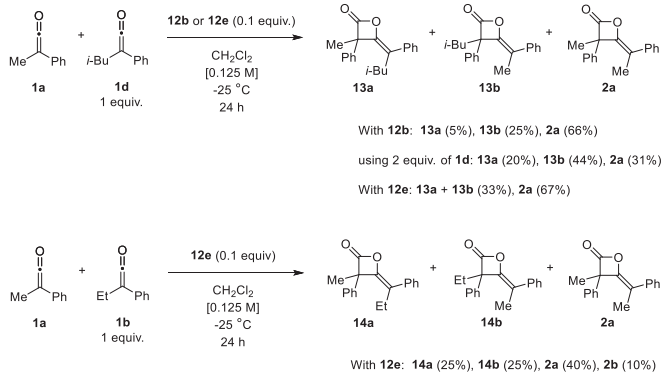
Josiphos derivative **12e** was determined to be the optimal catalyst with very good enantioselectivity of 90% ee being obtained (Table 1, entry 25). Excellent dimer:trimer selectivity was obtained after the reaction was diluted to 0.125 M concentration (ketene in CH_2Cl_2) (entries 24 and 25). The introduction of a more electron donating and sterically bulky *t*-Bu group at R^1 on Josiphos (**12d**) inhibited the reaction completely (entry 21). Interestingly, introduction of electron withdrawing and/or sterically bulky substituents at R^2 on the cyclopentadienyl phosphino group led to a small improvement (4% ee) in enantioselectivity (entry 22 vs entry 19). Cooling of the catalyst solution to −25 °C prior to addition to the cooled methylphenylketene solution led to a significant improvement in enantioselectivity (entry 25 vs entry 24). Lower and higher temperatures (e.g. −78 °C and 0 °C) than −25 °C had a negative effect on enantioselectivity (entries 16 and 17). Disappointingly, the employment of LiI as an additive was found to lead to an unclean and sluggish reaction (46% conv. after 24 h), in contrast to our earlier findings with the PBu_3/LiI catalytic system [11a,11c].

2.5. Scope of the phosphine-catalyzed enantioselective homodimerization reaction

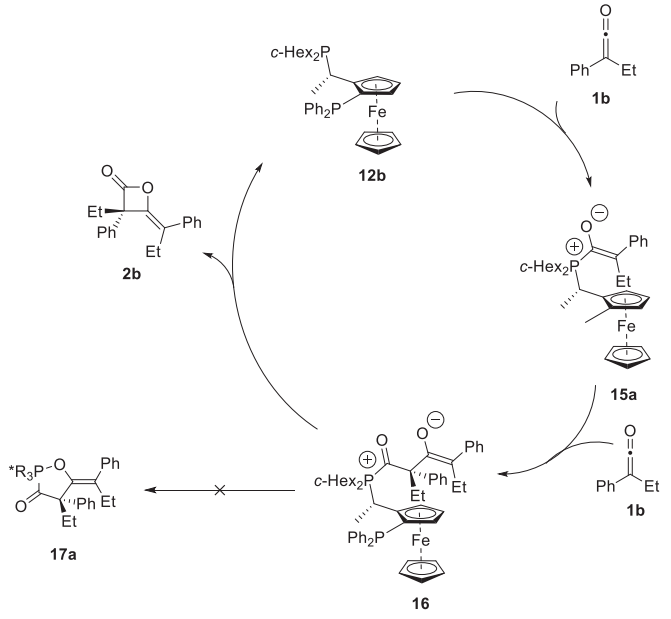
The substrate scope of the Josiphos-catalyzed methodology was then evaluated (Table 4). Simple extension of the R^2 alkyl substituent (to Et, and *n*-Bu) had little effect on reaction enantioselectivity or efficiency, provided the optimal Josiphos derivative was employed (entry 2 vs entries 4 and 7). However, if the R^2 substituent incorporated branching (e.g. Bn and *i*-Bu, entries 6 and 8), then a significant deleterious effect on reaction efficiency was observed. Those substrates possessing $R^2 = CH_3$ were homodimerized with optimal conversion and enantioselectivity (90–96% ee) using **12e** (Method C in Experimental). On the other hand, less reactive substrates, that possess more sterically demanding alkyl substituents (Et or *n*-Bu), were homodimerized more efficiently through the use of the less sterically hindered **12b** (Method D in Experimental). The latter reactions were conducted at a slightly higher concentration (0.25 M), without any increase in trimer formation (dimer:trimer ≥32:1).

Variation of the aromatic R^1 substituent was also tolerated with both *ortho*- and *para*-substituents (electron-donating or electron-withdrawing groups) working equally well in terms of affording good enantioselectivity. Significantly, the only other high-level enantioselective method for disubstituted ketene homodimerization, the N-heterocyclic carbene-catalyzed method of Ye's group, does not tolerate *ortho*-substituted substrates [14]. Heteroaromatic substituents such as thiophene were also tolerated, albeit with significantly lower enantioselectivity (46% ee, entry 13) presumably due to smaller steric size of R^1 substituent. In the case of the 3-thienyl substituent it was necessary to employ Binaphane in order to achieve useful levels of enantioselectivity (78% ee, entry 14). Dialkylketenes were also found to undergo homodimerization efficiently although the achiral 1,3-cyclobutanedione regioisomer was found to be the major isomer in most cases (entries 15–17), just as was observed with PBu_3 catalysis. Homodimerization of methyl isopropyl ketene also gave the 1,3-cyclobutanedione regioisomer, with only trace *β*-lactone being formed. The change in regioselectivity (relative to alkylarylketene homodimerization) likely arises from electron-donating dialkyl-substitution on the enolate, causing the enolate intermediate to cyclise through the C-atom rather than through the O-atom (Scheme 2).

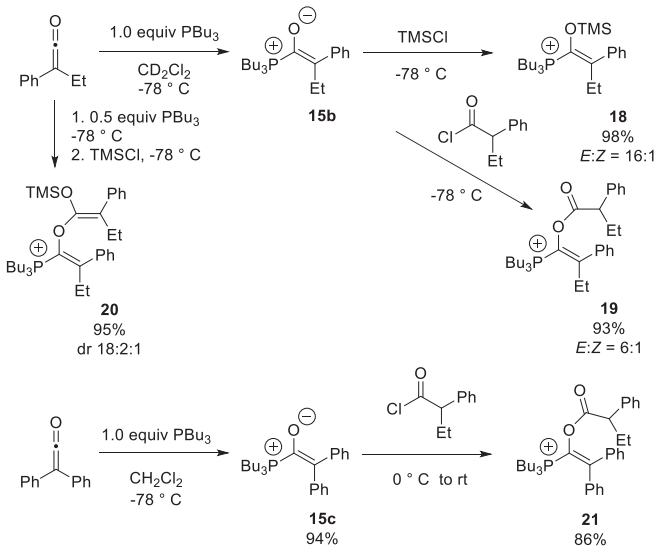
Ready access to both enantiomers of a given disubstituted ketene dimer through use of commercially available antipodes of Josiphos is a clear advantage of the phosphine-catalyzed methodology (Table 4, entry 1 vs entry 2, entry 3 vs entry 4) [18]. The major olefin isomer in each case (**2a**-**2p**) was determined to be the *Z*-isomer on the basis of previously reported X-ray crystal structure



Scheme 3. Regioselectivity in phosphine-catalyzed ketene heterodimerization.



Scheme 4. Initial mechanism proposed for Josiphos-catalyzed ketene homodimerization.



Scheme 5. Mechanistic experiments.

analysis of racemic **2a** (CCDC 794919), and for other compounds, by a comparison of spectroscopic data with that reported by Ye and co-workers [11d,14].

2.6. Development of the phosphine-catalyzed heterodimerization reaction

We noted from our homodimerization studies that Josiphos **12b** and **12e** did not affect homodimerization of isobutylphenylketene or diphenylketene (e.g. Table 4 entry 8). Indeed, ^{31}P NMR analysis revealed that there was no interaction between the phosphine catalyst **12b** and diphenylketene. Therefore, a strategy for heterodimerization involving slow addition (over 8 h) of a more reactive ketene (e.g. methylphenylketene) to a solution containing the catalyst and less reactive ketene (e.g. isobutylphenylketene) was explored (Scheme 3) [6]. This approach was successful to an extent, in that moderate regioselectivity (r.s. up to 5:1) in heterodimer formation was observed when there was a significant difference in reactivity between the proposed donor and acceptor ketenes, e.g. methylphenylketene vs isobutylphenylketene (Scheme 3, upper eq.). However, when the two ketenes possessed similar reactivity (electrophilicity), little or no regioselectivity was observed (Scheme 3, lower eq.).

2.7. In situ-generated ketene studies

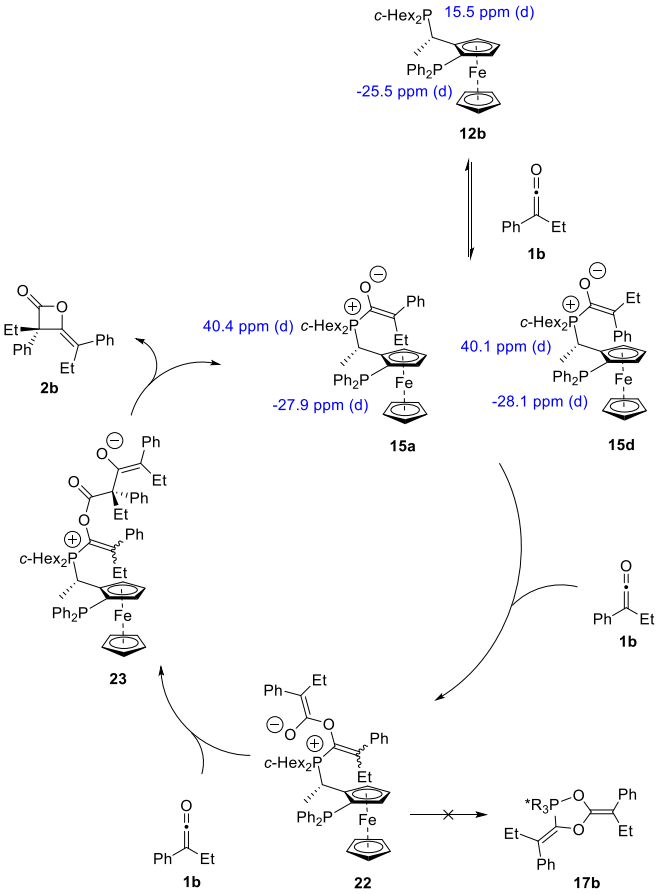
The availability of an in situ ketene generation variant would allow chemists to use commercially available acyl chlorides to assemble racemic and enantioenriched ketene homodimers, and thus bypass the need to isolate, purify and handle moisture-sensitive ketenes. To that end, the possibility of utilizing in situ-generated methylphenylketene for phosphine-catalyzed ketene homodimerization studies was investigated [6]. Methylphenylketene was generated through the addition of excess Me_2NEt to 2-phenylpropionyl chloride in THF (or toluene) at 0 °C. PBu_3 (0.2 equiv) was then added slowly to the reaction mixture. The reaction was then allowed to warm to room temperature overnight. Disappointingly, the isolated yield of desired ketene homodimer **2a** was modest, *ca.* 20–30%, and significantly lower compared to when pre-generated methylphenylketene was used (Tables 1 and 2).

2.8. Mechanism of the Josiphos-catalyzed dimerization reaction

We had previously proposed that Josiphos catalyzes the homodimerization reaction through a mechanism involving phosphonium enolate **15a** (Scheme 4) [11c]. Phosphonium enolate **15a** would be formed through addition of the di-*c*-hexylphosphino moiety of Josiphos **12b**/**12e** to the less sterically hindered side of the ketene **1b** to form an enolate **15a** in stereoselective fashion. With PBu_3 as catalyst, the stereoselectivity of enolate formation had been verified previously by ^{31}P NMR monitoring of the reaction with ethylphenylketene **1b** to give enolate **15b** (Scheme 5). An *E*:*Z* ratio of 7:1 for **15b** was measured, while kinetic trapping (in a separate experiment) with TMSCl provided a TMS enol ether derivative **18** with high stereoselectivity (dr 16:1, Scheme 5) [11d].

Phosphonium enolate **15a** would then react, through the C-atom or O-atom of the enolate, with another molecule of a ketene. In our initially proposed mechanism (Scheme 4), **15a** was anticipated to react with another molecule of ketene through C- of the enolate to give acylphosphonium **16**. 4-*Exo*-trig cyclisation would then afford ketene homodimer **2b** and allow for regeneration of catalyst **12b** [11c].

However, in the PBu_3-catalyzed homodimerization of diphenylketene (0.1 equiv of PBu_3 employed), a strong signal at 13.6 ppm was observed. The signal was subsequently revealed to be due to phosphonium enolate **15c**, after the enolate was generated in stoichiometric fashion and characterized (Scheme 5). Subsequently, strong evidence was obtained for a reaction mechanism involving **15c** as the true catalyst, where it reacts through the O-atom of the



Scheme 6. Revised mechanism proposed for Josiphos-catalyzed ketene homodimerization.

enolate [11d]. The in situ-formed catalyst **15c** was proposed to promote the homodimerization of diphenylketene by adding though the O-atom of the enolate, rather than through the C-atom of the enolate, to another molecule of ketene. Evidence for the propensity of phosphonium enolate **15** (**15b** or **15c**) to react through the O-atom with carbonyl substrates was obtained by examination of the reaction of enolates **15b** and **15c** with 2-phenylbutanoyl chloride. In both cases, the reaction proceeded primarily through the O-atom, as was confirmed by characterization of the ester products **19** and **21**, especially with the observation of an IR absorption band at 1761 and 1765 cm^{-1} respectively [11d]. The presence of the ester group in both derivatives was further confirmed by ^{13}C NMR spectra with signals observed at 170.0 and 171.2 respectively. **15c** was also independently generated and demonstrated to act as a catalyst (at 20 mol% loading) for the homodimerization of ethylphenylketene (95% yield).

Furthermore, TMSCl trapping of an intermediate formed in the reaction of PBu_3 with ethylphenylketene revealed the presence of a new *O*-acylated (rather than *C*-acylated) derivative **20**. This result strongly points towards a mode of reactivity involving reaction of **15** with ketenes through the O-atom of the enolate rather than through the C-atom.

In addition, acylphosphonium **16** (Scheme 4) would be expected to appear between 28 and 32 ppm in ^{31}P NMR spectra during reaction monitoring. The absence of such a signal, in PBu_3 and Josiphos-catalyzed ethylphenylketene homodimerization reactions, strongly suggested that the reaction does not proceed through an acylphosphonium intermediate [19].

Therefore, our revised proposal for the reaction mechanism is as follows: reaction of phosphonium enolate **15a** through the O atom of the enolate (*O*-acylation) with the carbonyl of another molecule of ketene leads to the formation of a second enolate intermediate **22** (Scheme 6). The latter 'ester' enolate intermediate adds to a third molecule of ketene to generate a new enolate intermediate **23**, which undergoes 4-*exo*-trig cyclisation to afford the desired ketene homodimer **2b** and regenerate enolate **15a**/**15d**. The assertion that the Josiphos-catalyzed homodimerization would involve a similar mechanism to that of the PBu_3-catalyzed reaction is justified when one considers the similar electronics of PBu_3 and the trialkylphosphine sidechain of Josiphos (Schemes 4–6). Moreover, the observation that isobutylphenylketene homodimer was formed as a side product (*ca.* 3–5%) during the heterodimerization reaction (Scheme 3), whereas none (0%) was formed during an attempted Josiphos-catalyzed homodimerization of isobutylphenylketene (Table 4 entry 8) supports the idea of an alternative catalytic cycle (i.e. not **15a** to **16**). A reasonable explanation would be that the phosphonium enolate catalyst **15** is more readily generated through the reaction of Josiphos with methylphenylketene than with the more sterically hindered isobutylphenylketene, and that the methylphenylketene-derived catalyst subsequently catalyzes the homodimerization of isobutylphenylketene. We have previously demonstrated the use of a phosphonium enolate **15c**, derived from diphenylketene and tri-*n*-butylphosphine, in promoting the homodimerization of ethylphenylketene, as well as the reaction of methylphenylketene with 4-chlorobenzaldehyde [11d,20].

^{31}P NMR data obtained through reaction monitoring at −30 °C and at −78 °C is also consistent with this new picture of the Josiphos-catalyzed homodimerization reaction. The ^{31}P NMR spectrum of Josiphos **12b** provided signals at 15.5 ppm (d, -P(*c*-Hex)$_2$) and at −25.5 ppm (d, -PPh_2). ^{31}P NMR monitoring at −78 °C of the **12b**-catalyzed homodimerization of ethylphenylketene revealed new signals at 40.5 ppm (d) and −28.4 ppm (d). On warming to −30 °C, ^{31}P NMR monitoring revealed signals at 40.4 ppm (d) (along with free diphenylphosphino group at −27.9 ppm (d)) and at 40.1 ppm (d) (along with free diphenylphosphino group at −28.1 ppm (d)). The signals between 40 and 41 ppm are consistent with tetravalent phosphonium species [19,21,22]. We propose that the signals at 40.4 ppm and 40.1 ppm represent the two possible enolate isomers **15a** and **15d** (Scheme 6). Both signals appeared approximately equal by integration (ratio = *ca.* 1.3:1) throughout the time of reaction monitoring at −30 °C, but the most intense signals were due to the free Josiphos catalyst **12b** (^{31}P NMR δ 15.5 (d), and −25.5 (d) ppm), with the ratio of **12b**: (**15a** + **15d**) = *ca.* 2:1. This shows that free Josiphos **12b** is the resting state of the catalyst (at least for the formation of ethylphenylketene dimer **2b**), and that conversion of **12b** to **15a** and **15d** represents the slow step of the reaction.

The formation of **15** as a mixture of *E*/*Z*-isomers does not mean that the ketene homodimer must be formed with low enantioselectivity. This is because the key enantioselectivity-determining step is that of 'ester' enolate **22** with ketene **1b** to give **23**. The Josiphos catalyst structure in **22** blocks the same face of the ester enolate, regardless of the olefin isomer geometry generated previously in **15**. In other words, interchanging the Et and Ph substituents in the phosphonium enol moiety of **22** does not affect sense of enantioselectivity significantly or change which enantioface becomes sterically hindered. Reaction of ester enolate **22** with ketene **1b** proceeds in a non-reversible fashion to afford intermediate **23**, which undergoes cyclisation to provide ketene dimer **2b** with high enantioselectivity (86–90% ee) and diastereoselectivity (*Z*:*E* > 32:1).

Finally, the absence of signals from the −50 to −120 ppm range in all ^{31}P NMR reaction monitoring experiments, conducted at a variety of temperatures, strongly suggests that the phosphine-catalyzed reactions avoid intermediacy of pentacovalent phosphorane species, such as **17a**/**17b** (Schemes 4 and 6), or at least that they are not formed in high enough concentrations to be detected by NMR spectroscopy. The electron-donating alkyl substituents (e.g. *c*-Hex) on the phosphonium centre of **22** would be expected to stabilize the positively charged phosphorus atom, making it less electrophilic, and hence disfavouring cyclisation to a pentacovalent phosphorane intermediate (Scheme 6) [21]. This is in contrast to an earlier mechanistic proposal by Bentrude's group for the $P(OMe)_3$-promoted homodimerization of dimethylketene, which involved a pentacovalent phosphorane intermediate of type **17b** [4d,4e]. The observation of such an intermediate in Bentrude's studies may be understood by taking into account the greater electrophilicity of a phosphite-derived phosphonium centre, and hence the greater susceptibility to nucleophilic attack by enolate oxygen.

3. Conclusion

Details of extensive optimisation studies revealed that tri-*n*-butylphosphine is the optimal catalyst for promoting non-enantioselective homodimerization of a range of alkylarylketenes and dialkylketenes. On occasion lithium iodide was found to be a useful additive in suppressing ketene trimerization. For the asymmetric ketene homodimerization reaction, Josiphos derivatives were found to give the best results, frequently providing the desired β-lactone ketene dimer in ≥90% ee. Studies on the development of a phosphine-catalyzed heterodimerization of two disubstituted ketenes were less successful, with the desired ketene heterodimer being formed in modest yield and with moderate regioselectivity. Mechanistic studies involving intermediate trapping experiments and extensive ^{31}P NMR analysis suggested that an in situ-generated phosphonium enolate was acting as the true catalyst of the dimerization reactions but we cannot rule out the possibility that an equilibrium amount of free phosphine is the true active catalyst.

4. Experimental section

4.1. General information

All reactions were carried out in flame dried glassware under a nitrogen atmosphere using standard inert atmosphere techniques unless otherwise stated. Diethyl ether and THF were dried using sodium benzophenone stills, CH_2Cl_2 and toluene were dried using calcium hydride stills, methanol was dried using a magnesium methoxide still, and *N*,*N*-dimethylethylamine was distilled from potassium hydroxide under nitrogen [23]. (*R*)-1-[(S_p)-2-(Diphenylphosphino)ferrocenyl]-ethyldicyclohexyl phosphine, (*S*)-1-[(R_p)-2-(Diphenylphosphino)ferrocenyl]ethyl-dicyclohexylphosphine, (*S*)-1-{(R_p)-2-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]ferrocenyl}ethyldicyclohexylphosphine, (*R*)-1-{(S_p)-2-[Bis[3,5-bistrifluoromethyl)phenyl]phosphino]ferrocenyl}ethyldicyclohexylphosphine were purchased from Aldrich Chemical Co. and Strem Chemicals and used as received. (*R*)-Binaphane, tri-*n*-butyl phosphine, lithium iodide, *n*-butyllithium (2.5 M in hexane), and $LiAlH_4$ (1.0 M in Et_2O) were purchased from Aldrich Chemical Co. and used as received. Iatrobeads (Bioscan, 6RS-8060, 60 μM particle size) and TLC plates (Sorbent Technologies, UV254, 250 μM) were used as received. Methylphenylketene, methyl-4-tolylketene, methyl-2-tolylketene, ethyl-4-tolylketene, methyl-2-chlorophenylketene, ethylphenylketene, ethyl-4-chlorophenylketene, ethyl(3-thiophenyl)ketene, *n*-butylphenylketene, isobutylphenylketene, benzylphenylketene, diphenylketene, *c*-hexyl methyl ketene, ethyl *c*-hexyl ketene and dimethylketene were prepared according to literature procedures [24].

NMR spectra were recorded on a Bruker DPX Avance 200 spectrometer (200 MHz for ^1H and 50 MHz for ^{13}C) and on a Bruker Biospin AG 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) for ^1H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra. IR spectra were recorded on a Bio Rad FTS-175C spectrometer. Optical rotations were measured on a Rudolph DigiPol 781 TDV automatic polarimeter.

Low resolution mass spectra were recorded on a GC-MS Hewlett Packard HP 6890 GC instrument with a 5973 mass selective detector. High resolution mass spectra were obtained from the College of Sciences Major Instrumentation Cluster at Old Dominion University. Analytical high performance liquid chromatography (HPLC) was performed using a Daicel Chiralpak AD column (0.46 cm × 25 cm), a Daicel Chiralpak AS-H column (0.46 cm × 25 cm) and a Daicel Chiralcel OD-H column (0.46 cm × 25 cm) (Daicel Chemical Ind., Ltd.) on a PerkinElmer 235C instrument attached with diode array detector (deuterium lamp, 190–600 nm) with HPLC-grade isopropanol and hexanes as the eluting solvents.

Racemic ketene dimers **2a**-**2n** and achiral cyclobutanediones **4q** and **4o** were prepared and characterized as previously described [11a,11d]. Enantioenriched **2a**-**2p** were prepared and characterized as previously described [11c]. Phosphonium enolate trapping products **18**–**21** were prepared and characterized as previously described.[11d] ^{31}P NMR Spectra for **15c** and **18**–**21** are found in the Electronic Supplementary Information.

4.2. Determination of enantiomeric excesses, dimer: trimer ratios (Tables 1–4) and Z: E olefin ratios

Enantiomeric excesses were determined by assaying the β-lactones **2a**-**2p** using chiral HPLC analysis (at λ = 254 or 225 nm; details given for each compound). Authentic racemic samples for chiral HPLC analysis were generated through the PBu_3-catalyzed reaction [11a]. the absolute configurations of **2a**, **2b**, **2j**, and **2p** were assigned on the basis of a comparison of specific rotation values with literature values [11c]. the absolute configurations of **2c** and **2g**-**2l** were assigned by analogy. The dimer: trimer ratios (Tables 1–4) were determined for the crude products by ^1H NMR analysis or by comparing the peak areas of GC-MS data. The major diastereomer of **2a**-**2p** was determined to be the *Z*-isomer through comparison with literature spectroscopic data, and by X-ray crystal structure analysis of racemic **2a** (CCDC 794919) [11d]. The *Z*:*E* olefin ratio for **2a**-**2p** was determined to be > 32:1 by GC-MS analysis of the crude β-lactones.

4.3. Synthetic procedures

4.3.1. Synthesis of racemic β-lactones by homodimerization of ketoketenes

4.3.1.1. Method A for homodimerization 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 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. Following filtration of the drying agent, aqueous H_2O_2 solution (50%, 2 drops) was added to the CH_2Cl_2 solution and stirred for 10 min at room temperature. The solvent was removed under reduced pressure to provide the crude product for ^1H NMR/GC-MS 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 GC-MS and HPLC analysis and confirmed by ^1H and ^{13}C NMR spectroscopy.

4.3.1.2. Method B for homodimerization of ketoketenes. To a solution of ketoketene (0.62 mmol, 1 equiv) in CH_2C_{l2} (1.2 mL, 0.5 M), tri-*n*-butylphosphine (0.06 mmol, 0.1 equiv) was added at 0 °C. The reaction was stirred at the indicated temperature for the indicated time. The reaction was then quenched by the addition of aqueous H_2O_2 solution (50%, 2 drops) and stirred for 10 min at room temperature. The solvent was removed under reduced pressure to provide the crude product for ^1H NMR/GC-MS 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 the solvent was removed under reduced pressure to yield the desired ketoketene dimer in high purity (≥95%), in most cases, as determined by GC-MS and HPLC analysis and confirmed by ^1H and ^{13}C NMR spectroscopy.

4.3.1.3. Method C for asymmetric homodimerization of methyl substituted ketoketenes. Ketoketene (0.34 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.2 mL) and cooled to −25 °C. (*S*)-1-{(*R*p)-2-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]ferrocenyl}ethyldicyclohexylphosphine or (*R*)-1-{(*S*p)-2-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]ferrocenyl}ethyldicyclohexylphosphine (0.03 mmol, 0.1 equiv) was dissolved in CH_2Cl_2 (0.5 mL), and was then transferred via syringe to the flask containing the ketoketene solution. The resulting solution (0.125 M of ketoketene in solvent) was stirred for 24 h at −25 °C before being briefly warmed to room temperature. The reaction was then quenched by the addition of

aqueous H_2O_2 solution (50%, 2 drops) at room temperature. After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The crude product was dissolved in 10% EtOAc/hexane (5 mL) and dichloromethane (1 mL). The resulting solution was passed through a plug column of neutral silica (iatrobeads, 2 × 2 cm, 4 g) [50 x weight of reaction mixture]. The plug column was eluted with 10% EtOAc/hexane (100 mL), and the solvent was removed under vacuum to furnish the desired ketoketene dimer with ≥95% purity in most cases (as determined by GC-MS and 1H NMR analysis). Further purification was carried out in some cases as specified.

4.3.1.4. Method D for asymmetric homodimerization of ketoketenes. Ketoketene (0.31 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1 mL) and cooled to −25 °C. (*R*)-1-[(*S*p)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine or (*S*)-1-[(*R*p)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (0.03 mmol, 0.1 equiv) was dissolved in CH_2Cl_2 (0.35 mL), cooled to −25 °C in most cases (exceptions: formation of **2l** and **4o**), and was then transferred via syringe to the flask containing the ketoketene solution. The resulting solution (0.25 M of ketoketene in solvent) was stirred for 24 h at −25 °C before being briefly warmed to room temperature. The reaction was then quenched by the addition of aqueous H_2O_2 solution (50%, 2 drops) at room temperature. After stirring for 10 min at room temperature, the solvent was removed under reduced pressure. The crude product was dissolved in 10% EtOAc/hexane (5 mL) and dichloromethane (1 mL). The resulting solution was passed through a plug column of neutral silica (iatrobeads, 2 × 2 cm, 4 g) [50 x weight of reaction mixture]. The plug column was eluted with 10% EtOAc/hexane solvent system (100 mL), and the solvent was removed under vacuum to furnish the desired ketoketene dimer with ≥95% purity in most cases (as determined by GC-MS and ^{1}H NMR analysis). Further purification was carried out in some cases as specified.

4.3.1.5. Method E for asymmetric homodimerization of ketoketenes. Ketoketene (0.34 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.35 mL) and was cooled to −78 °C. (*R*)-Binaphane (0.03 mmol, 0.1 equiv) was dissolved in CH_2Cl_2 (0.35 mL) and cooled to −78 °C. The phosphepine solution was then transferred via syringe to the flask containing the ketoketene solution. The reaction was stirred at −78 °C for 48 h, after which the solvent was removed under reduced pressure. The crude product was treated with dry isopropanol (3 mL) to dissolve the crude ketoketene dimer and precipitate the phosphepine. The mixture was filtered under nitrogen using a Schlenk filter funnel. The precipitate was washed with dry isopropanol (2 × 3 mL), the phosphine was recovered, and the solvent was removed from the filtrate under reduced pressure. The crude product was then dissolved in 5% EtOAc/hexane (6 mL) and CH_2Cl_2 (1.5 mL), before being passed through a plug of neutral silica (3.3 g). Elution with 5% EtOAc/hexane (60 mL), followed by solvent removal under reduced pressure furnished the desired ketoketene dimer with ≥95% purity in most cases (as determined by GC-MS and ^{1}H NMR analysis). Further purification was carried out in some cases as specified.

*4.3.1.6. Z-3-Methyl-3-phenyl-4-(1-phenyl-ethylidene)-oxetan-2-one ((±)-**2a**).* Method A was followed. Methylphenylketene **1a** (270 mg, 2.05 mmol), stirred for 2 h at 0 °C, and was isolated as a colorless oil (221 mg, 82%); 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.

*4.3.1.7. Z-3-Ethyl-3-phenyl-4-(1-phenyl-propylidene)-oxetan-2-one ((±)-**2b**).* Method A was followed. Ethylphenylketene **1b** (160 mg, 1.09 mmol), stirred for 4 h at 0 °C, was isolated as a colorless oil (135 mg, 84%); IR (thin film): 1857, 1699, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.42−7.20 (m, 10H), 2.38−2.02 (m, 4H), 1.15 (t, *J* = 7.4 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9, 143.9, 135.4, 134.7, 129.3, 128.6, 128.6, 128.2, 127.6, 126.5, 116.5, 70.1, 26.3, 22.9, 12.8, 10.0; MS (EI 70 eV): *m*/*z* 292, 146, 117, 103, 91, 77; $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{20}H_{20}O_2Na$: 315.1355; found: 315.1351.

*4.3.1.8. Z-3-Butyl-3-phenyl-4-(1-phenylpentylidene)-oxetan-2-one ((±)-**2c**).* Method B was followed. *n*-Butylphenylketene **1c** (108 mg, 0.62 mmol), stirred for 1.5 h at 0 °C, was isolated as a colorless oil (108 mg, >99%); IR $_{\nu\ max}$ (thin film): 1869, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38−7.19 (m, 10H), 2.30−2.19 (m, 2H), 2.12−2.04 (m, 2H), 1.61−1.36 (m, 2H), 1.28−1.02 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.86−0.74 (m, 4H), 0.69 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 144.8, 135.6, 135.1, 129.3, 128.6, 128.5, 128.2, 127.6, 126.5, 115.3, 69.3, 32.9, 30.4, 29.5, 27.6, 23.0, 22.8, 14.1, 14.0; MS (EI 70 eV): *m*/*z* 348, 264, 205, 174, 131, 117, 103; $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{24}H_{28}O_2Na$: 371.1982; found: 371.1984.

*4.3.1.9. Z-3-Benzyl-4-(1,2-diphenylethylidene)-3-phenyloxetan-2-one ((±)-**2e**).* Method B was followed. Benzylphenylketene **1e** (111 mg, 0.53 mmol), stirred for 5 h at room temperature. Crude **2e** was obtained with 64% conversion as determined by GC-MS analysis; MS (EI 70 eV): *m*/*z* 416, 281, 208, 179.

*4.3.1.10. Z-3-(2-Chlorophenyl)-4-(1-(2-chlorophenyl)ethylidene)-3-methyloxetan-2-one ((±)-**2g**).* Method B was used. Methyl-2-chlorophenylketene **1g** (60 mg, 0.36 mmol), stirred for 1.5 h at 0 °C, was isolated as a colorless oil (60 mg, >99%); IR $_{\nu\ max}$ (thin film): 1891, 1843, 1725, 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.48−7.12 (m, 8H), 2.06 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 145.7, 136.0, 134.9, 133.4, 132.0, 131.5, 130.7, 130.3, 130.0, 129.3, 128.8, 127.5, 127.1, 108.5, 62.1, 20.0, 16.1; MS (EI 70 eV): *m*/*z* 332, 166, 138, 103; $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{18}H_{14}Cl_2O_2Na$: 355.0263; found: 355.0266.

*4.3.1.11. Z-3-Methyl-3-o-tolyl-4-(1-o-tolylethylidene)oxetan-2one ((±)-**2h**).* Method B was used. Methyl-2-tolylketene **1h** (50 mg, 0.34 mmol), stirred for 1 h at 0 °C, was isolated as a colorless oil (49 mg, 97%); IR $_{\nu\ max}$ (thin film): 1883, 1844, 1717, 1456, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.43−7.10 (m, 8H), 2.26 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 145.3, 137.7, 136.8, 136.0, 133.1, 132.7, 130.6, 128.7, 128.5, 128.0, 127.1, 126.6, 126.1, 110.3, 63.3, 20.6, 20.5, 19.9, 17.5; MS (EI 70 eV): *m*/*z* 292, 264, 249, 146, 117, 91; $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{20}H_{20}O_2Na$: 315.1356; found: 315.1359.

*4.3.1.12. Z-3-Ethyl-3-thiophen-3-yl-4-(1-thiophen-3-yl-propylidene)-oxetan-2-one ((±)-**2l**).* Method A was used. Ethyl-3-thiophenylketene **1l** (162 mg, 1.06 mmol), stirred for 7 h at 0 °C, isolated as a colorless oil (127 mg, 78%); IR $_{\nu\ max}$ (thin film): 1859, 1695, 1411 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.30−7.16 (m, 4H), 7.05−7.02 (m, 2H), 2.39−2.01 (m, 4H), 1.09 (t, *J* = 7.3 Hz, 3H), 0.92 (m, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.1, 144.5, 136.1, 135.4, 127.4, 127.1, 126.1, 125.5, 122.6, 122.4, 111.3, 67.5, 26.1, 22.6, 13.5, 9.7; MS (EI 70 eV): *m*/*z* 247, 152, 123, 97; $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{16}H_{16}O_2S_2Na^+$: 327.0484; found: 327.0485.

*4.3.1.13. 2,4-Dicyclohexyl-2,4-diethylcyclobutane-1,3-dione (**4o**).* Method A was used. Ethyl *c*-hexyl ketene **1o** (52 mg, 0.34 mmol), stirred at 0 °C to room temperature overnight. Crude **4o** was

purified by passing through a plug of neutral silica (iatrobeads), eluting with 3% EtOAc/hexane. The solvent was removed under reduced pressure to yield **4o** as a colorless oil (45 mg, 87%), and as an inseparable mixture of diastereomers (*cis*:*trans* = 1:1 as determined by NMR analysis); IR $_{\nu\ max}$ (thin film): 1754, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) for both diastereomers: δ 2.11–2.05 (m, 4H), 1.74–1.51 (m, 32H), 1.19–1.02 (m, 16H), 0.88 (t, J = 7.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) for both diastereomers: δ 171.5, 171.5, 55.0, 55.0, 40.0, 40.0, 31.3, 31.3, 30.6, 30.6, 26.5, 26.5, 22.3, 22.3, 12.2, 12.2; MS (EI 70 eV): *m*/*z* 304, 153, 125, 83; HRMS analysis obtained for 1,3-diol derivative (through $LiAlH_4$ reduction of **4o**) $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{20}H_{32}O_2Na$: 331.2608; found: 331.2607.

*4.3.1.14. Z-3-Ethyl-3-p-tolyl-4-(1-p-tolyl-ethylidene)-oxetan-2-one ((±)-**2j**).* Method B was used. Ethyl-4-tolylketene **1j** (77 mg, 0.48 mmol), stirred for 5 h at 0 °C, was isolated as a colorless oil (77 mg, >99%); IR $_{\nu\ max}$ (thin film): 1862, 1734, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.30–7.12 (m, 8H), 2.34–2.22 (m, 2H), 2.29 (s, 3H), 2.29 (s, 3H), 2.11–2.05 (m, 2H), 1.14 (t, J = 7.4, 3H), 0.84 (t, J = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 143.8, 138.3, 137.3, 132.5, 131.8, 129.9, 129.3, 128.1, 126.3, 116.1, 69.8, 26.2, 22.8, 21.4, 21.2, 12.8, 9.9; MS (EI 70 eV) *m*/*z* 320, 263, 160, 132, 117; $(M + Na)^+$ HRMS *m*/*z* calcd for $C_{22}H_{24}O_2Na$: 343.1669; found: 343.1667.

*4.3.1.15. (S,Z)-3-Methyl-3-phenyl-4-(1-phenyl-ethylidene)-oxetan-2-one ((−)-**2a**).* Method C was used. To a cooled solution of methylphenylketene (510 mg, 3.85 mmol) in CH_2Cl_2 (28 mL) was added a solution of (*S*)-1-{(*Rp*)-2-[bis[3,5-bis(trifluoromethyl)phenyl] phosphino]ferrocenyl}ethyldicyclohexylphosphine (333 mg, 0.39 mmol) in CH_2Cl_2 (3 mL). (−)-**2a** was isolated as a colorless oil (331 mg, 65%); HPLC analysis: 94% ee [Daicel Chiralpak AD column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 5.0 min (minor), 6.6 min (major)]; $[\alpha]_D$ = −68.3 (c = 0.41, $CHCl_3$); IR (thin film) 1881, 1844, 1699, 1140 cm-1; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.50–7.10 (m, 10H), 1.90 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 146.9, 136.2, 135.2, 129.3, 128.6, 128.6, 127.6, 127.4, 126.2, 108.6, 64.4, 19.6, 15.5; 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.

4.3.1.16. Kinetic experiments on tri-n-butylphosphine-catalyzed homodimerization of isobutylphenylketene. To a constant concentration of isobutylphenylketene in CH_2Cl_2 (0.1 M) was added a varied number of equivalents of PBu_3 (0.01, 0.035, 0.05, 0.1, and 0.2 equiv.) at room temperature. The reaction was monitored every 30, 70, 115, 200 min by GC-MS analysis to determine the rate of product **2d** formation (Fig. 1).

Tri-*n*-butylphosphine (0.1 equiv.) was added to different concentrations of isobutylphenylketene (0.05, 0.1, 0.15, 0.25, 0.5 M) in CH_2Cl_2 at room temperature. Each reaction was monitored individually for the amount of product **2d** formed every 30, 70, 115, 200 min by GC-MS analysis (Fig. 2).

From the GC-MS traces, the relative areas of the ketene **1d** (a known starting amount of ketene was used as the standard for calculations) to that of the dimer product **2d** were used to determine the number of mmol of ketene and ketene dimer in the mixture at any given time. See the Supporting Information for Tables showing details of kinetic experiments such as the average rate of product formed (mmol/min) at the various time intervals.

4.3.1.17. In situ generation of methylphenylketene for ketene homodimer synthesis. 2-Phenylpropionyl chloride (253 mg, 1.5 mmol) was dissolved in THF (3 mL), and the solution was cooled to 0 °C. *N*,*N*-dimethylethylamine (0.66 mL, 6.0 mmol) was then added slowly to the cooled solution over 10 min to give a yellow-coloured mixture. Tri-*n*-butylphosphine (76 μL, 0.3 mmol) was added slowly to the cooled reaction mixture over 1 min. The reaction was then allowed to warm to room temperature overnight. The reaction mixture was filtered through a plug of silica gel eluting with 30% EtOAc/hexane to afford crude product solution. Further purification of the crude product through flash column chromatography eluting with a gradient system (hexane to 1%–2% EtOAc/hexane), followed by solvent removal under reduced pressure furnished the desired ketoketene dimer **2a** (47 mg, 24%). A similar yield (42%, composed of dimer:trimer = *ca.* 2:1) was obtained when the reaction was conducted in toluene.

4.3.1.18. Procedure for phosphine-catalyzed ketene heterodimerization. Methylphenylketene **1a** (51 mg, 0.38 mmol) in CH_2Cl_2 (0.8 mL) was added over 8 h to a solution of isobutylphenylketene **1d** (55 mg, 0.38 mmol) and phosphine **12b** (25 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) at −25 °C. The reaction was then stirred at −25 °C for 15 h. GC-MS analysis of the crude product showed 30% ketene heterodimer (5:1 ratio of heterodimers **13b**:**13a**), and 66% methylphenylketene homodimer **2a**; ^1H NMR (400 MHz, $CDCl_3$, TMS) for major regioisomer δ 7.55–6.91 (m, 10H), 2.27 (dd, J = 14.3, 6.3 Hz, 1H), 2.05–1.99 (m, 1H), 2.01 (s, 3H), 1.64–1.51 (m, 1H), 0.77 (d, J = 6.6 Hz, 3H), 0.60 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for major regioisomer δ 171.6, 147.4, 135.5, 135.0, 129.3, 128.6, 128.5, 128.3, 127.6, 126.4, 113.9, 63.6, 38.4, 26.1, 22.4, 22.2, 19.6; MS (EI 70 eV): *m*/*z* 306 (**13b**).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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