JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

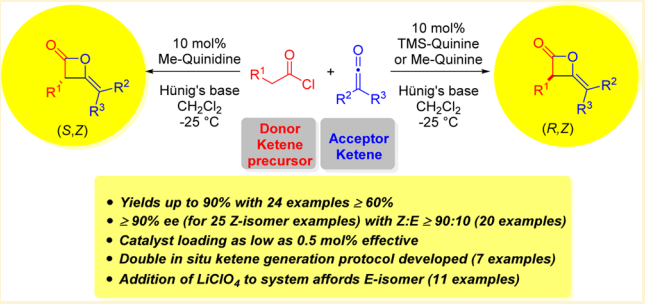
Catalytic Asymmetric Synthesis of Ketene Heterodimer β-Lactones: Scope and Limitations

Shi Chen, Ahmad A. Ibrahim, Nicholas J. Peraino, Divya Nalla, Mukulesh Mondal, Maxwell Van Raaphorst, and Nessan J. Kerrigan*

Department of Chemistry, Oakland University, 2200 North Squirrel Road, Rochester, Michigan 48309-4477, United States

Supporting Information

ABSTRACT: In this article we describe extensive studies of the catalytic asymmetric heterodimerization of ketenes to give ketene heterodimer β-lactones. The optimal catalytic system was determined to be a cinchona alkaloid derivative (TMS-quinine or Me-quinidine). The desired ketene heterodimer β-lactones were obtained in good to excellent yields (up to 90%), with excellent levels of enantioselectivity (≥90% ee for 33 *Z* and *E* isomer examples), good to excellent (*Z*)-olefin isomer selectivity (≥90:10 for 20 examples), and excellent regioselectivity (only one regioisomer formed). Full details of catalyst development studies, catalyst loading investigations, substrate scope exploration, protocol innovations (including double in situ ketene generation for 7 examples), and an application to a cinnabaramide A intermediate are described. The addition of lithium perchlorate (1−2 equiv) as an additive to the alkaloid catalyst system was found to favor formation of the *E* isomer of the ketene heterodimer. Ten examples were formed with moderate to excellent (*E*)-olefin isomer selectivity (74:25 to 97:3) and with excellent enantioselectivity (84−98% ee).



INTRODUCTION

Historically, the goal of developing methods for selective ketene heterodimerization (cross-dimerization of two different ketenes) to provide access to ketene heterodimer β-lactones has proved an elusive target (Scheme 1).[1−6] Given the extensive use of enantioenriched β-lactones in synthetic activities, we were motivated to address this problem.[5,7−9] The obstacles to the attainment of such a goal have included the difficulty of achieving regioselective formation of the desired ketene heterodimer (two possible ketene heterodimer β-lactones), competing ketene homodimerization (two possible ketene homodimer β-lactones), and inability to control exocyclic olefin stereoselectivity (*E* vs *Z* isomer).[6] Finally, the ability to access one enantiomer of the desired ketene heterodimer β-lactone has become an important and necessary target, especially if the ketene heterodimerization reaction is to be considered a viable method for natural product and drug molecule synthetic applications.

Recently, we reported the first method to address all of these difficulties in a practical manner (Schemes 1 and 2).[10] We determined that an alkaloid derivative catalytic system was capable of effecting a regioselective and enantioselective heterodimerization of ketenes to provide access to ketene heterodimer β-lactones in up to 99% ee, with excellent regioselectivity (only one ketene heterodimer observed), and with very good to excellent olefin stereoselectivity (*Z*:*E* up to >97:3). Key to the success of our protocol was the slow addition of the more reactive ketene precursor (donor ketene precursor) to a solution containing the less reactive ketene (acceptor ketene) and the alkaloid catalyst (Scheme 2). In that way regioselective ketene heterodimerization was ensured, while donor ketene homodimerization was limited or reduced to a manageable level. We found that acceptor ketene homodimerization was never an issue if a ketene of attenuated reactivity was chosen for the acceptor role: e.g. an alkylarylketene, diarylketene, dialkylketene, or TMS-ketene.

In this article we disclose full details of our catalyst optimization/development studies, catalyst loading investigations, and substrate scope evaluation as well as an exploration of a double in situ ketene generation variant, olefin stereoselectivity studies (switching selectivity to favor *E* isomer), and stereochemical models.

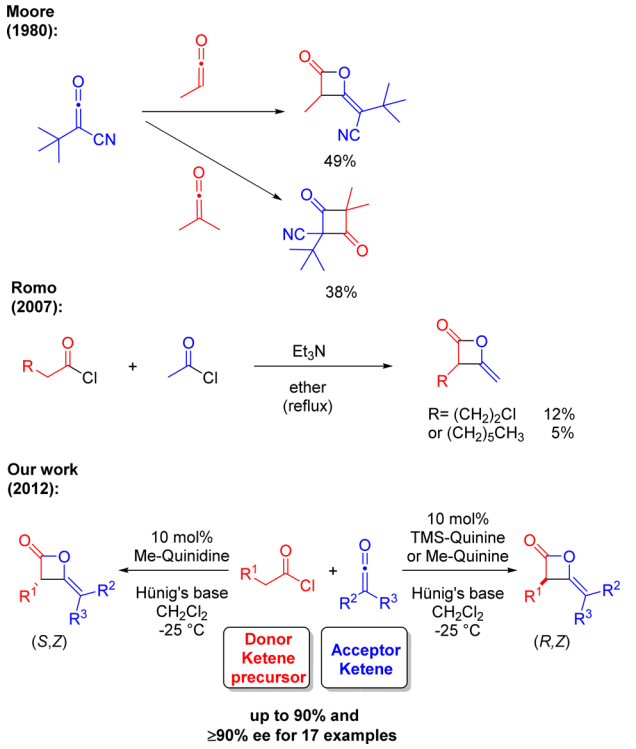
RESULTS AND DISCUSSION

We began our optimization of the ketene heterodimerization methodology with the goal of preparing methylphenylketene-derived heterodimer (*Z*)-**3a** in high enantiomeric excess (Table 1). This involved examining the reaction of methylphenylketene, which would act as the less reactive ketene (*acceptor ketene*), with methylketene (generated in situ from propionyl chloride), which would act as the more reactive ketene (*donor ketene*). We had previously had success in developing a disubstituted ketene (ketoketene) homodimerization reaction and related reactions through the use of phosphine catalysis.[11] However, phosphine catalysts (Binaphane, Josiphos, and PBu_3) were found to be too

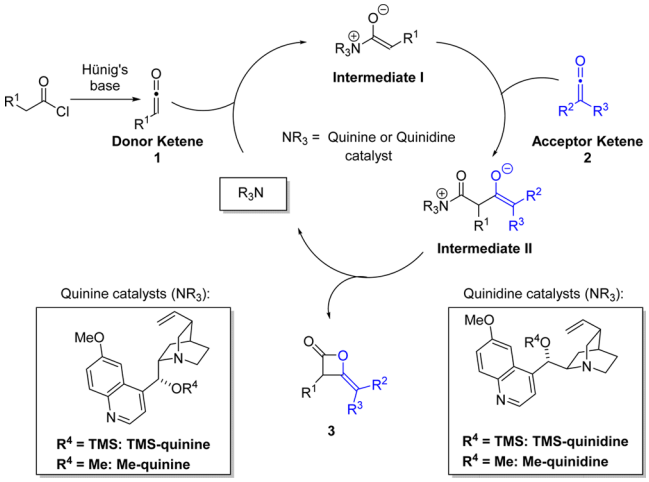
Received: June 21, 2016
Published: August 4, 2016

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

Scheme 1. Development of Ketene Heterodimerization

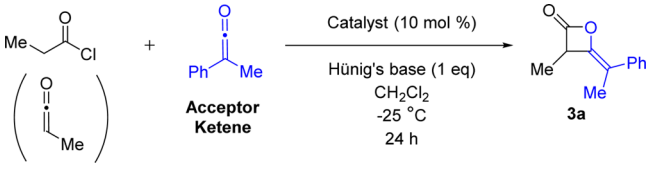


Scheme 2. Initial Mechanistic Proposal for Catalytic Asymmetric Heterodimerization of Ketenes



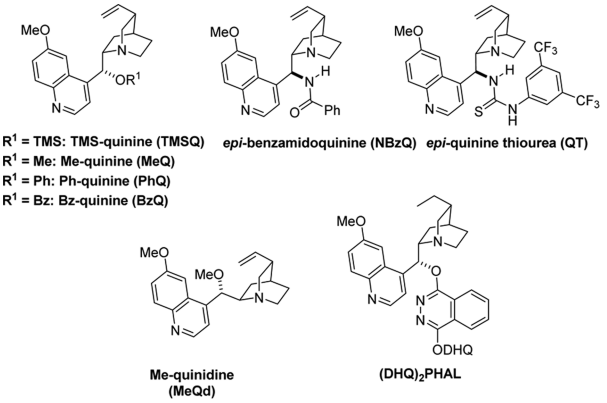
active to facilitate the desired heterodimerization, leading generally to oligomerization of the donor ketene or suffering from catalyst deactivation under in situ ketene generation conditions. Inspired by Calter's work on the alkaloid-catalyzed ketene homodimerization reaction, we proceeded to evaluate cinchona alkaloid derivatives as promoters of the ketene heterodimerization reaction.[12−14] During control experiments it became apparent that the alkaloid catalysts were incapable of catalyzing the homodimerization of less reactive ketenes (methylphenylketene or dimethylketene) to any great extent (<10% conv at best). This outcome suggested to us a strategy for promoting a selective ketene heterodimerization reaction: the alkaloid catalyst would be mixed with a less reactive ketene (the *acceptor ketene*, e.g. a disubstituted ketene or TMS-ketene) and Hünig's base, and a solution of a more reactive ketene or

Table 1. Optimization of Reaction Conditions in Alkaloid-Catalyzed Heterodimerization of Ketenes[a]



entry	catalyst	addition time of AcCl (h)	solvent	yield (%) (conversn (%))	ee (%)[b]
1	TMSQ	1	THF	0	
2	TMSQ	1	CH_2Cl_2	(40)	nd
3[c]	MeQ	1	CH_2Cl_2	(50)	nd
4[d]	MeQ	1	CH_2Cl_2	(65)	nd
5	MeQ	8	CH_2Cl_2	65	83[e]
6	TMSQ	8	CH_2Cl_2	57	94[e]
7	$(DHQ)_2PHAL$	8	CH_2Cl_2	38	93
8	QT	8	CH_2Cl_2	<5	nd
9	NBzQ	8	CH_2Cl_2	43	13
10	PhQ	8	CH_2Cl_2	39	61
11	BzQ	8	CH_2Cl_2	55	72
12	MeQd	8	CH_2Cl_2	64	98[e]
13	MeQd	8	THF	47	91
14	MeQd	8	$PhCH_3$	35	89
15	MeQd	8	CH_2Cl_2 (−78 °C)	50	91
16	MeQd	8	CH_2Cl_2 (0 °C)	20	36
17	MeQd	8	CH_2Cl_2 (room temp)	15	5

[a]Only one heterodimer regioisomer observed by GC-MS and ^{1}H NMR analysis of crude for entries 5,6 and 12 (*Z*:*E* ratio >97:3 as determined by GC-MS and ^{1}H NMR analysis). Definitions of catalysts:



[b]ee determined by chiral HPLC. [c]Entries 1−3: 0.13 M concentration of acceptor ketene in solvent. [d]Entries 4−17: 0.25 M concentration of acceptor ketene in solvent. [e]MeQ and TMSQ afforded the *R* enantiomer of **3a**, while MeQd provided the *S* enantiomer of **3a**.

acyl chloride precursor (the *donor ketene*) would be added slowly to the reaction solution (Scheme 2). In this way, donor ketene homodimerization would be minimized, as the donor ketene would be generated slowly over time and as a result kept in low concentrations at all times. Regioselective heterodimerization would also be enabled, as the more reactive donor ketene would be more likely to form the critical ammonium enolate intermediate. Once donor ketene ammonium enolate formation occurred, it would encounter an excess amount of acceptor ketene molecules rather than donor ketene molecules, and hence a regioselective ketene heterodimerization would be favored. An enantioselective reaction would also be expected,

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

given the high enantioselectivity observed in Calter's alkaloid-catalyzed homodimerization of methylketene and alkaloid-catalyzed reaction of monosubstituted ketenes with a variety of electrophiles (e.g., with iminoesters in Lectka's β-lactam synthesis).[7c,13]

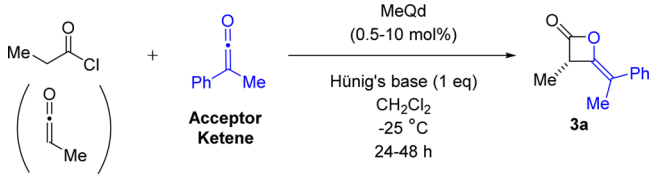
Early in optimization, we determined that it was essential to add propionyl chloride over 8 h via syringe pump to a CH_2Cl_2 solution of methylphenylketene, the alkaloid catalyst (Me-quinidine or Me-quinine/TMS-quinine), and Hünig's base, in order to achieve optimal yields of the desired ketene heterodimer (ca. 60−65%) (Table 1, entries 5, 6, and 12). This reaction setup minimized competing methylketene homodimerization.

Many alkaloid catalysts used in this study were prepared through one-step literature procedures described by the groups of Calter (TMSQ and TMSQd), Gaunt (MeQ and MeQd), and Lectka (BzQ), while others were commercially available ($(DHQ)_2PHAL$).[12−14] TMS- and Me-protected alkaloid catalysts were determined to provide very good to excellent enantioselectivity in ketene heterodimerization, with TMS-quinine (TMSQ) or Me-quinine (MeQ) providing access to the *R* enantiomer, and the pseudoenantiomeric Me-quinidine (MeQd) providing access to the *S* enantiomer (Table 1, entries 5, 6, and 12). Surprisingly, bifunctional catalysts possessing a H-bonding donor group as well as the nucleophilic quinuclidine nitrogen (e.g., benzamidoquinine and thiourea-quinine catalyst, entries 8 and 9) provided poor enantioselectivity and reactivity. Ph-quinine and Lectka's Bz-quinine provided lower levels of asymmetric induction in comparison to Me-quinine or TMS-quinine (entries 10 and 11) and were not explored further.

CH_2Cl_2 was found to be superior to all other reaction solvents (e.g., toluene and THF) in facilitating optimal conversion to the desired ketene heterodimer (Table 1, entry 12 vs entries 13 and 14). However, it was notable that very good levels of enantioselection could be obtained in most solvents examined (e.g., entries 12−14: 89−98% ee). The best levels of enantioselectivity were observed when the reaction was conducted at −25 °C (entry 12), while significantly lower enantioselectivity was observed at 0 °C (entry 16) and virtually racemic product was obtained when the reaction was conducted at room temperature (entry 17). We speculate that Hünig's base-mediated racemization of the ketene heterodimer occurs more readily at temperatures above −25 °C. A control experiment involving the subjection of enantioenriched ketene heterodimer **3a** (94% ee) to typical reaction conditions at room temperature for 24 h seemed to confirm this hypothesis, as significant racemization had occurred (ee decreased to 15%). For the optimized examples (entries 5, 6 and 12), complete regioselectivity for the desired ketene heterodimer **3a**, as determined by GC-MS and ^{1}H 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) (entries 5, 6, and 12).

The level of catalyst loading was examined for the Me-quinidine case. Remarkably, it was determined that the reaction could be run at as low as 0.5 mol % loading (Table 2, entry 5) without significant reduction in yield of ketene heterodimer, albeit with somewhat attenuated enantioselectivity (82% ee vs 98% ee for 10 mol % loading). A reasonable compromise of acceptable yield and enantioselectivity (52% yield and 93% ee) may be attained if a loading of 2.5 mol % is employed (Table 2, entry 3).

Table 2. Catalyst Loading Studies in Alkaloid-Catalyzed Heterodimerization of Ketenes[a]



entry	catalyst loading (mol %)	reaction time (h)	yield (%)	ee (%)[b]	*Z*:*E*[c]
1	10	24	64 (87)[d]	98	>97:3
2	5	24	72	94	96:4
3	2.5	24	52	93	96:4
4	1	24	57	87	97:3
5	0.5	48	53	82	96:4

[a]Only one heterodimer regioisomer observed in all cases by GC-MS and ^{1}H NMR analysis of crude. [b]ee determined by chiral HPLC. [c]*Z*:*E* ratio determined by GC-MS analysis. [d]4 mmol scale.

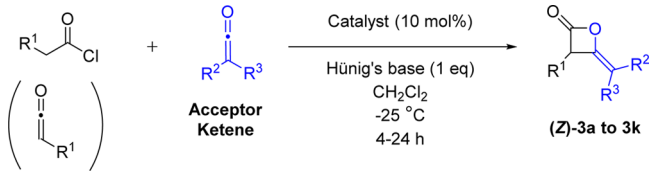
We then proceeded to evaluate the substrate scope of the reaction through variation of both the acceptor ketene and donor ketene structure (Table 3). Significant variation in donor ketene structure was tolerated, with methylketene, ethylketene, *n*-propylketene, *n*-butylketene, and acetoxyketene all working well. However, benzyloxyketene, phenoxyketene, *N*-phthaloylketene, and isopropylketene failed as donor ketenes for various reasons, including incomplete ketene generation under the reaction conditions (isopropylketene) and oligomerization of the ketene under the reaction conditions (e.g., benzyloxyketene). A variety of alkylarylketenes, including methylphenylketene, ethylphenylketene, *n*-butylphenylketene, dimethylketene, diphenylketene, and TMS-ketene (see Table 4) were found to function as effective acceptor ketenes. However, dialkylketenes as acceptor ketenes gave mixed results; therefore, although dimethylketene performed excellently as an acceptor ketene (Table 3, entries 8, 9, 22, and 23), cyclohexylmethylketene, isopropylmethylketene, and isobutylmethylketene generally gave lower yields (20−40%) and variable levels of olefin stereoselectivity (*Z*:*E* = ca. 1:1 to 7:1).

In most cases, good to excellent enantioselectivity was obtained (70 to >99% ee), with good to excellent levels of olefin isomer selectivity (*Z*:*E* from 84:16 to >97:3 for 17 examples). Occasionally lower enantioselectivity (e.g., 73% ee for Table 3, entry 3) was encountered when Me-quinine was used as the catalyst, and this was attributed to the sterically smaller O-methylated group providing reduced enantiofacial shielding of the ammonium enolate intermediate I (Scheme 2). This situation could be rectified by substituting TMS-quinine for Me-quinine, leading to significantly higher enantioselectivity (e.g., 93% ee for entry 4 vs 73% for entry 3), albeit at the cost of lower yield (33%, entry 13) or lower *Z*:*E* selectivity (74:26 for entry 13).

In the case of ethylphenylketene (Table 3, entries 3 and 4), the relatively lower (*Z*)-olefin isomer stereoselectivity may be due to reversible protonation−deprotonation of putative intermediate II by the ammonium salt of Hünig's base (Scheme 2). Interestingly the level of isomerization appears to have some dependence on the catalyst used (90:10 for MeQ vs 69:31 for TMSQ, entries 3 and 4). Subjecting ketene heterodimer (+)-**3b** (*Z*:*E* = 90:10) to standard reaction conditions (TMS-quinine, propionyl chloride, Hünig's base, at −25 °C in the presence or absence of $LiClO_4$) did not lead to any significant change in

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

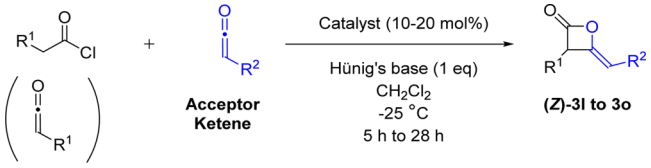
Table 3. Substrate Scope of Heterodimerization of Monosubstituted Ketenes with Disubstituted Ketenes[a]



entry	(+)-/(−)-3	cat.	R^1	R^2	R^3	yield (%)	ee (%)[b]	Z:E[c]
1	(+)-**3a**[d]	TMSQ	Me	Ph	Me	57	94	>97:3
2	(−)-**3a**	MeQd	Me	Ph	Me	64 (87)[e]	98	>97:3
3	(+)-**3b**	MeQ	Me	Ph	Et	57	73	90:10
4	(+)-**3b**	TMSQ	Me	Ph	Et	60	93	69:31
5	(−)-**3b**	MeQd	Me	Ph	Et	62	98	84:16
6	(−)-**3c**	TMSQ	Me	Ph	Ph	61	96	
7	(+)-**3c**	MeQd	Me	Ph	Ph	60	96	
8	(+)-**3d**[f–h]	MeQ	Me	Me	Me	79	91	
9	(−)-**3d**[f–h]	MeQd	Me	Me	Me	90	95	
10	(+)-**3e**	TMSQ	Et	Ph	Me	43	>99	>97:3
11	(−)-**3e**	MeQd	Et	Ph	Me	40	>99	>97:3
12	(+)-**3f**	MeQ	Et	Ph	Et	73	70	91:9
13	(+)-**3f**	TMSQ	Et	Ph	Et	33	80	74:26
14	(−)-**3f**	MeQd	Et	Ph	Et	65	95	87:13
15	(*R*)-**3g**	MeQ	*n*-Pr	Ph	Et	61[i]	72	93:7
16	(*S*)-**3g**	MeQd	*n*-Pr	Ph	Et	37[i]	95	83:17
17	(*R*)-**3h**	MeQ	*n*-Bu	Ph	Me	54	74	>97:3
18	(*R*)-**3h**	TMSQ	*n*-Bu	Ph	Me	55	88	97:3
19	(*S*)-**3h**	MeQd	*n*-Bu	Ph	Me	64	94	>97:3
20	(*R*)-**3i**	MeQ	*n*-Bu	Ph	Et	51[i]	76	93:7
21	(*S*)-**3i**	MeQd	*n*-Bu	Ph	Et	43	95	84:16
22	(+)-**3j**[j]	MeQ	OAc	Me	Me	52	76	
23	(−)-**3j**[j]	MeQd	OAc	Me	Me	57	91	
24	(+)-**3k**[k]	MeQd	Me	TMS	Me	50	nd	78:22

[a]Only one heterodimer regioisomer observed in all cases by GC-MS analysis of crudes and NMR analysis of **3**. [b]ee determined by chiral HPLC. [c]*Z*:*E* ratio determined by GC-MS or ^{1}H NMR analysis. [d]Sign of specific rotation: + enantiomer or − enantiomer. [e]Reaction conducted on 4 mmol scale. [f]In these cases 2 equiv of $LiClO_4$ was used as an additive. [g]Isolated as Weinreb amide derivative **4** due to volatility of heterodimer. [h]20 mol % of catalyst used. [i]Isolated yield for two steps after conversion to acid **5** through Pd/C-catalyzed hydrogenolysis (characterized as acid; see the Supporting Information and ref 20 for details). [j]Isolated as Weinreb amide **4** due to susceptibility to decomposition on silica gel. [k]1 equiv of $LiClO_4$ was used as an additive.

Table 4. Scope of Alkaloid-Catalyzed Heterodimerization of Two Monosubstituted Ketenes



entry	(+)-/(−)-3[a]	catalyst	R^1	R^2	yield (%)[b]	ee (%)[c]
1	(+)-**3l**	TMSQ	Me	TMS	67	95
2	(−)-**3l**	MeQd	Me	TMS	75	98
3[d]	(−)-**3m**	TMSQ	Cl-Et	TMS	44	97
4[d]	(+)-**3m**	MeQd	Cl-Et	TMS	49	98
5[d]	(−)-**3n**	TMSQ	*n*-Hex	TMS	53	97
6[d]	(+)-**3n**	MeQd	*n*-Hex	TMS	55	95
7	**3o**	MeQd	*n*-Hex	H	(18)[e]	nd

[a]Sign of specific rotation: + enantiomer or − enantiomer. [b]Only 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. [c]ee determined by chiral HPLC or GC. [d]20 mol % of catalyst used. [e]Percent conversion by GC-MS to desired ketene heterodimer, not isolated.

Z:*E* selectivity, ruling out isomerization of olefin geometry in the heterodimer product.

For dimethylketene-derived ketene heterodimers (Table 3 entries 8 and 9), it was found necessary to carry out heterodimerizations in the presence of $LiClO_4$ (2 equiv) in order to limit competing homodimerization of methylketene. For most examples (e.g., entries 1−7) an excess of donor ketene acyl chloride (2.0 equiv) was used to effect full conversion to the desired ketene heterodimer. As a result, the amount of ketene homodimer formed as a side product for the latter examples ranged from ca. 20−40% conversion (by GC-MS analysis of crudes). On the other hand, for examples requiring equimolar to excess molar amounts of acceptor ketene (e.g., entries 8, 9, 22, and 23, requiring only 0.5−1.0 equiv of acyl chloride), <1% donor ketene homodimer was afforded, as determined by GC-MS analysis of the crude products. Formation of ketene homodimer derived from acceptor ketene was never observed in any of our studies. Furthermore, only one heterodimer regioisomer was observed in all cases, as determined by GC-MS and ^{1}H NMR analysis of the crudes.

Having determined that the ketene heterodimerization reaction was very efficient at providing access to heterodimers derived from the reaction of monosubstituted ketenes with disubstituted ketenes, we were motivated to investigate the more daunting challenge of cross-dimerization of two monosubstituted

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

ketenes (Table 4). Such heterodimers had already received some attention for use in applications toward the synthesis of complex molecules (e.g., salinosporamide A by Romo's group), and so a method that would provide enantioselective access to this class of heterodimer would be expected to have immediate applications.[5] For this purpose we sought an acceptor ketene that would be unlikely to undergo homodimerization or indeed to act as a donor ketene and so issues over the control of regioselectivity and acceptor ketene homodimerization would be eliminated. We had previously found that TMS-ketene was incapable of undergoing catalytic homodimerization under either alkaloid or even phosphine catalysis. We surmised that the failure of homodimerization under nucleophile-catalyzed conditions was due to the low reactivity of onium enolate intermediate I (Scheme 2) derived from TMS-ketene. The well-precedented stabilization of α anions by silicon was presumed to be the underlying reason for the low reactivity of the onium enolate.[15] In light of the failed homodimerization results, TMS-ketene appeared to be an ideal candidate for the role of acceptor ketene, provided it could be subjected to reaction with a more reactive ammonium enolate (intermediate I). This was proven, as TMS-ketene was found to perform excellently in its role as acceptor ketene to provide access to heterodimers derived from methylketene, 2-chloroethylketene, and *n*-hexylketene (Table 4, entries 1−6). All of the desired ketene heterodimers were formed with excellent enantioselectivity and complete regioselectivity (Table 4, entries 1−6).

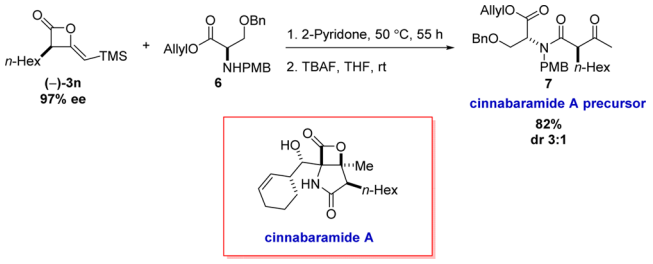
In some cases (Table 4, entries 3 and 4), yields somewhat lower (44−49%) than those for previous heterodimerizations were obtained, due to competing homodimerization of the donor ketene. The actual amount of donor ketene homodimer formed depended upon the amount of acyl chloride used. Not surprisingly, most homodimer (comprising 20−40% of crude product) was formed in those reactions where an excess of donor ketene acyl chloride (up to 2 equiv) was employed (Table 4, entries 1−4). The least amount of donor ketene homodimer (<10% of crude product) was observed in those cases where an excess of acceptor ketene (up to 2 equiv) was used (entries 5 and 6). The use of less donor ketene and slower addition (12 h for entries 5 and 6) of the acyl chloride precursor acted to minimize the formation of homodimer. Conveniently, donor ketene homodimer (e.g., methylketene homodimer in entries 1 and 2) was volatile enough to be removed under high vacuum in many cases. Alternatively, the desired heterodimer was separated from donor ketene homodimer (e.g., entries 3 and 4) by flash column chromatography through a plug of neutral silica (see the Experimental Section for details).

The advantage of using pregenerated TMS-ketene as acceptor ketene (entries 1−6) was emphasized as follows. Cross-dimerization of two simple in situ generated monosubstituted ketenes (*n*-hexylketene with ketene) led to a complex mixture of homodimers and heterodimers, with the desired ketene heterodimer accounting for only 18% of the product mixture (as determined by GC-MS analysis, Table 4 entry 7).

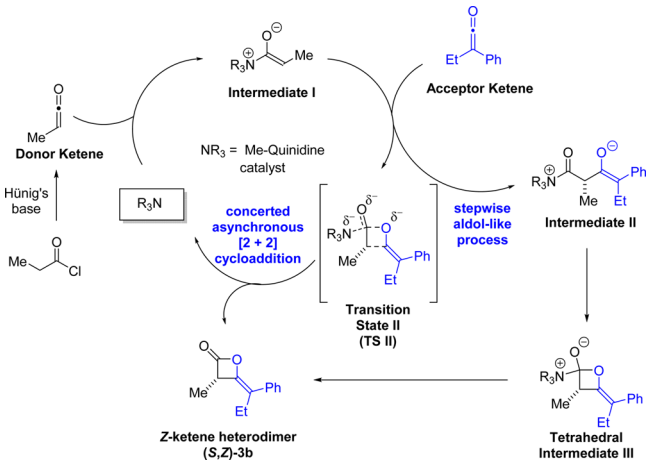
Heterodimers **3m**,**n** were of particular interest, given their anticipated potential as intermediates for the synthesis of salinosporamide A and cinnabaramide A.[5] A cinnabaramide A intermediate was efficiently accessed through ring opening of ketene heterodimer (−)-**3h** with a serine derivative (Scheme 3).

Reaction Mechanism. Possible intermediates in the catalytic cycle for the formation of ketene heterodimer (*S*,*Z*)-**3b** are depicted in Scheme 4. Density functional theory

Scheme 3. Application of Enantioenriched Ketene Heterodimer to Synthesis of Cinnabaramide A Intermediate



Scheme 4. Mechanism for Formation of *Z* Isomer



(B3LYP/6-31+G(d,p) level of theory) was employed to calculate reaction coordinates for the methyl quinidine catalyzed heterodimerization of methylketene with ethylphenylketene (to give ketene heterodimer (*S*,*Z*)-**3b**).[16,17]

In our earlier communication we proposed a mechanism (Schemes 2 and 4) where an ammonium enolate (intermediate I) would be formed stereoselectively as the (*Z*)-enolate due to the alkaloid catalyst (Me-quinidine) adding to the less sterically hindered side of the methylketene.[10] Our more recent calculations (see the Supporting Information) support this proposal and are in qualitative agreement with the results of Lectka's earlier molecular mechanics study on alkaloid-catalyzed β-lactam formation.[13,16] The free energy of the (*Z*)-enolate (intermediate I) was found to be 8.86 kcal mol^{-1} lower in energy then the (*E*)-enolate, indicating that essentially all of the first enolate exists in the *Z* isomer form. From there we considered a number of possibilities for the reaction of intermediate I ((*Z*)-enolate) with the acceptor ketene (ethylphenylketene). One mechanistic route involves an aldol-type process which gives rise to ammonium enolate (intermediate II), and following lactonization, (*S*,*Z*)-**3b** is afforded (Schemes 2 and 4). Alternatively, the reaction may proceed through a concerted asynchronous [2 + 2] cycloaddition of intermediate I with ethylphenylketene, via transition state II (TS II) (Scheme 4).[18] Precedent for concerted substitution (rather than stepwise addition−elimination) at the carbonyl of certain carboxylic acid derivatives is known and has been proposed when a good leaving group is bonded to the carbonyl.[19]

Stereochemical Models. We propose that enantioselection is determined in the transition state for the reaction of the ammonium enolate (intermediate I) with ethylphenylketene (Figure 1). Calculations showed that approach of

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

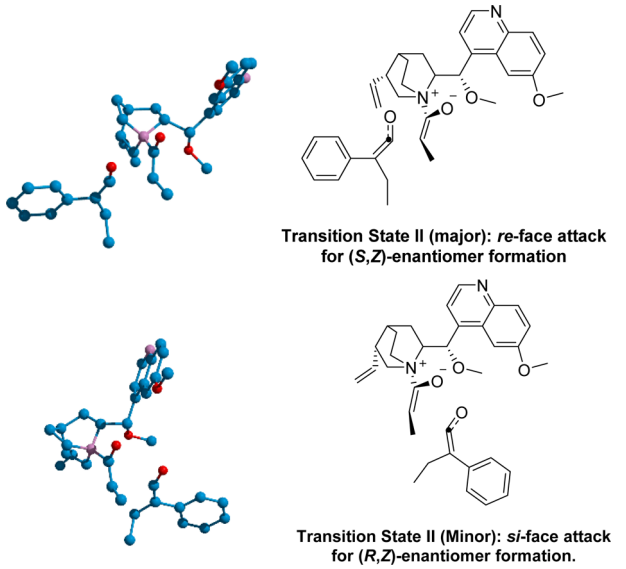


Figure 1. Stereochemical model: calculated transition states II for formation of (*Z*)-ketene heterodimer.

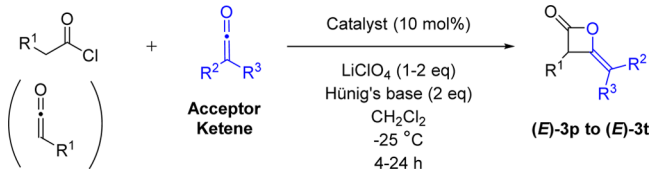
ethylphenylketene to the *re* face of the ammonium enolate of intermediate I (*Z* isomer) was nearly 2 kcal mol^{-1} lower in energy than the competing *si* face approach (Figure 1, transition state II *re* face and *si* face). This corresponds well with the observed enantioselectivity of 98% ee for formation of (−)-**3b** (Table 3, entry 5). The formation of a significant amount of *E* isomer (16% for (−)-**3b**) in the reaction may be rationalized by a transition state which is calculated to be just 0.65 kcal mol^{-1} higher in energy than transition state II *re* face leading to (*Z*)-ketene heterodimer (see the Supporting Information). Again, this energy difference (predicting a *Z*:*E* ratio of 79:21) correlates well with the experimentally determined *Z*:*E* ratio of 84:16 for the formation of (*Z*)-(−)-**3b** (Table 3, entry 5).

Synthesis of (*E*)-Ketene Heterodimers. Having the potential to access both olefin isomers of a given heterodimer would be useful for synthetic applications involving different diastereomers of dipropionate or deoxypropionate derivatives.[8e,20] Interestingly, when $LiClO_4$ (1−2 equiv) was added to the catalytic system, we noted a change in olefin geometry selectivity from favoring the *Z* isomer to favoring formation of the *E* isomer (e.g., Table 3, entries 3 and 5, in comparison with Table 5, entries 1 and 2).[21] A number of other lithium salt additives and Lewis acids (LiI, LiBr, LiCl, $LiBF_4$, $ZnCl_2$, and $MgCl_2$) were investigated, but none of them gave results as good as those with lithium perchlorate. The desired products were generally obtained in >70% yield, with *Z*:*E* selectivity ranging from 26:74 to 3:97 and with good to excellent enantioselectivity (84−98% ee). The best levels of (*E*)-olefin selectivity were obtained for isobutylphenylketene as acceptor ketene, presumably due to the greater steric bulk of the isobutyl group in comparison to the unbranched ethyl or *n*-butyl group (Table 5, entries 5, 6, 9, and 10 vs entries 1−4, 7, and 8). Unfortunately, the procedure failed for the synthesis of (*E*)-ketene heterodimers derived from methylphenylketene, with low olefin isomer selectivity being obtained (e.g., for **3a**, *Z*:*E* = 66:34).

We surmise that the role of $LiClO_4$ is to stabilize enolate intermediates (Scheme 5). Due to the intermediacy of a relatively long lived lithium enolate intermediate II, it is possible for equilibration of olefin geometry to occur (Scheme 5). We propose that the change in olefin selectivity involves equilibration of the second enolate intermediate (intermediate II) through reversible protonation−deprotonation by protonated Hünig's base/Hünig's base to afford mainly the *E* isomer of intermediate II. Subsequent lactonization via tetrahedral intermediate III would provide the ketene heterodimer as the *E* isomer.

Double in Situ Ketene Generation. From a practical standpoint the availability of a double in situ ketene generation variant, which would preclude the need to pregenerate and handle the acceptor ketene, would be highly desirable. Such a process would allow chemists to use two commercially available acyl chlorides to assemble enantioenriched ketene heterodimers and thus bypass the need to isolate, purify, and handle

Table 5. Asymmetric Synthesis of (*E*)-Ketene Heterodimers[a]

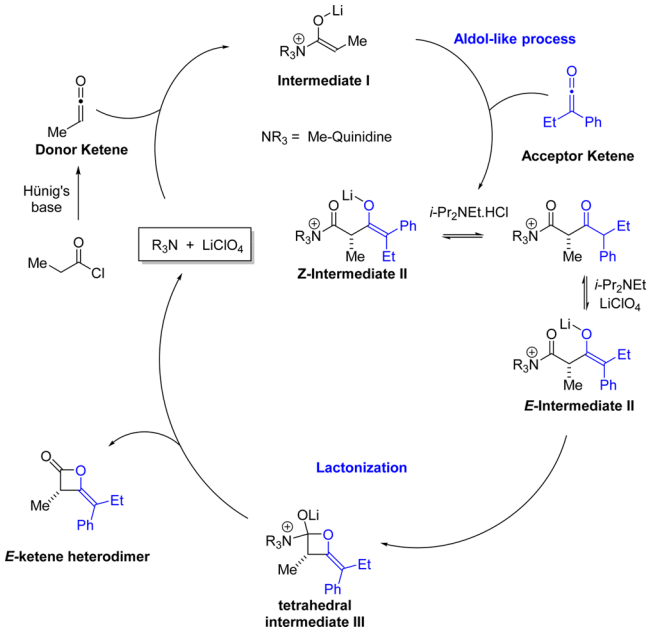


entry	(+)-/(−)-3[b]	catalyst	R^1	R^2	R^3	yield (%)	ee (%)[c]	*Z*:*E*[d]
1	(+)-**3p**	TMSQ	Me	Et	Ph	56	85	16:84
2	(−)-**3p**	MeQd	Me	Et	Ph	57	94	13:87
3[e]	(+)-**3q**	TMSQ	Me	*n*-Bu	Ph	69	84	24:76
4[e]	(−)-**3q**	MeQd	Me	*n*-Bu	Ph	78	92	26:74
5	(+)-**3r**	TMSQ	Me	*i*-Bu	Ph	78	96	4:96
6	(−)-**3r**	MeQd	Me	*i*-Bu	Ph	83	98	3:97
7	(+)-**3s**	TMSQ	Et	Et	Ph	86	93	26:74
8	(−)-**3s**	MeQd	Et	Et	Ph	86	88	24:76
9[e]	(−)-**3t**	TMSQ	Et	*i*-Bu	Ph	76	97	6:94
10[e]	(+)-**3t**	MeQd	Et	*i*-Bu	Ph	88	98	5:95

[a]Only one heterodimer regioisomer observed in all cases by GC-MS analysis of crudes and NMR analysis of **3**. [b]Sign of specific rotation: + enantiomer or − enantiomer. [c]ee determined by chiral HPLC. [d]*Z*:*E* ratio determined by GC-MS analysis of crudes and confirmed by ^{1}H NMR analysis. [e]In these cases 1 equiv of $LiClO_4$ was used as an additive.

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

Scheme 5. Proposed Mechanism for Formation of *E* Isomer



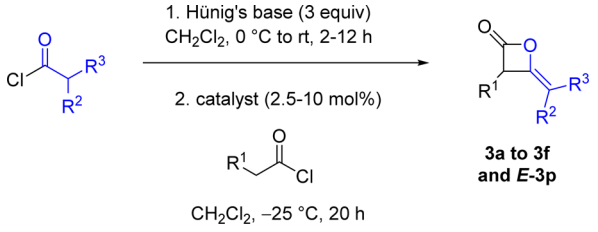
moisture-sensitive acceptor ketenes. In situ generation of the acceptor ketene as well as of the donor ketene was investigated for seven different examples (Table 6). (−)-**3a** was formed with comparable yield (61%) and with slightly lower enantiomeric excess (91% ee) in comparison to those when pregenerated methylphenylketene was used (Table 6, entry 1 vs Table 3, entry 2). Indeed, in all cases examined high enantioselectivity (>90% ee) comparable to that obtained using pregenerated acceptor ketene was observed (Table 6 vs Table 3). Significantly, the reaction could be performed with a lower catalyst loading (2.5 mol %), without any decrease in yield, diastereoselectivity, or enantioselectivity (Table 6, entry 2). However, for examples involving ethylphenylketene as acceptor ketene, a longer ketene generation time was required (12 h at room temperature), in order to provide reasonable yields (35−48%) of the desired ketene heterodimer (Table 6, entries 4, 6, and 7). Even with this modification, a distinct drop in yield was noted due to incomplete acceptor ketene generation. Overall, these results demonstrate the great promise of the method and suggest that the scope of the process could be increased in the future to include more exotic nonisolable acceptor ketenes.

Applications. To demonstrate that ketene heterodimers **3** can act as surrogates for aldol construction, (−)-**4d** (derived from **3d**) underwent a highly diastereoselective reduction through reaction with KEt_3BH to afford *β*-hydroxyamide (+)-**8d** with excellent diastereoselectivity (dr >99:1), and with virtually no loss of enantiomeric integrity (94% ee) (Scheme 6).[10,22] In addition, we have recently demonstrated that ketene heterodimers may be conveniently converted into *anti*-deoxypropionate derivatives **5**, through a simple Pd/C-catalyzed hydrogenolysis procedure (Scheme 6).[20] Such structural motifs have found widespread use in the synthesis of polyketide natural products and drug molecules. Moreover, simple deoxypropionate derivatives often possess interesting intrinsic biological activity.[23,24] For example, (+)-**5a** was readily reduced to alcohol (+)-**9a** (93%, dr 4:1), a molecule which displays biological activity in its own right (Scheme 6).[23]

CONCLUSION

In summary, we have developed a catalytic asymmetric heterodimerization of ketenes of wide substrate scope that allows even two different *mono*substituted ketenes to be cross-dimerized with excellent enantioselectivity (33 examples with ≥90% ee), good to excellent (*Z*)-olefin isomer selectivity (84:16 to >99:1), and excellent regioselectivity (only one heterodimer formed in all cases). Moderate to excellent (*E*)-olefin isomer selectivity (74:25 to 97:3) along with excellent enantioselectivity (84−98% ee) could also be accomplished through use of lithium perchlorate as an additive. Catalyst loading studies suggest that the reaction can be run on as a low a loading as 0.5 mol %, without significant reduction in yield and only slight reduction in enantioselectivity, which is very competitive in comparison to other organocatalytic processes.[25] Furthermore, a double in situ ketene generation protocol displays promise, as seven examples proceeded with excellent enantioselectivity and moderate to good yields. Studies are currently underway to

Table 6. Double in Situ Generation of Ketenes[a]

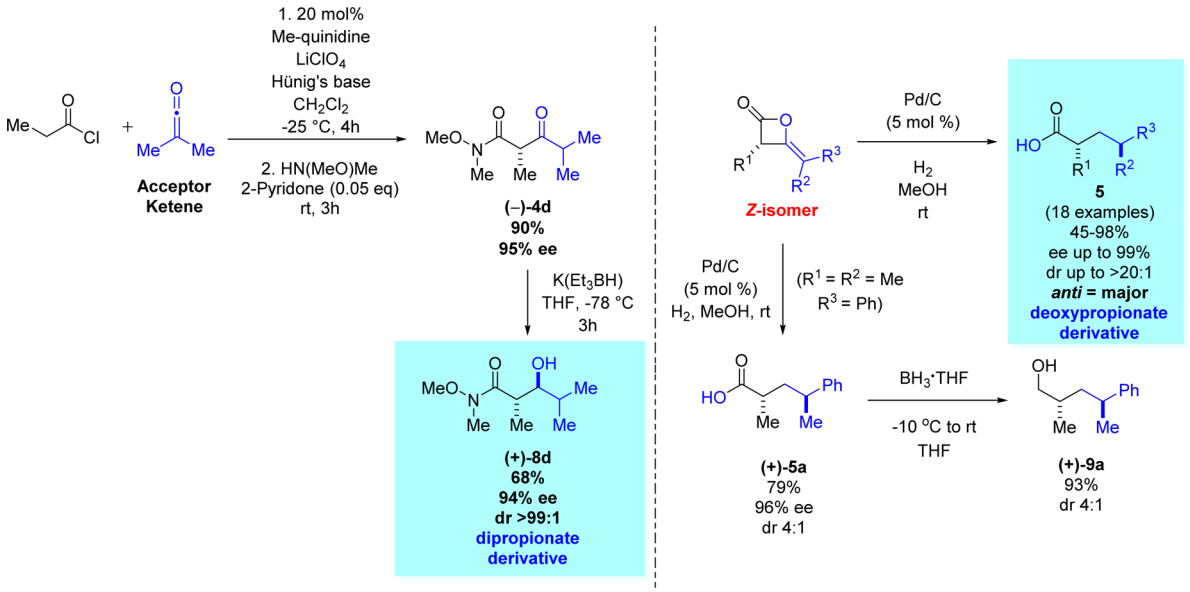


entry	catalyst (amt (mol %))	R^1	R^2	R^3	yield (%)[b]	ee (%)[c]	*Z*:*E*[d]	**3**
1	MeQd (10)	Me	Me	Ph	61	91	>97:3	(−)[e]-**3a**
2	MeQd (2.5)	Me	Me	Ph	74	92	99:1	(−)[e]-**3a**
3	TMSQ (10)	Me	Me	Ph	67	93	99:1	(+)[e]-**3a**
4	MeQd (10)	Me	Et	Ph	48	95	78:22	(−)-**3b**
5	MeQd (10)	Et	Me	Ph	71	97	98:2	(−)-**3e**
6	MeQd (10)	Et	Et	Ph	35	97	86:14	(−)-**3f**
7	MeQd (10)[f]	Me	Ph	Et	41	>99	33:67	(*E*)-(−)-**3p**

[a]Only one heterodimer regioisomer observed in all cases by GC-MS analysis of crudes and NMR analysis of **3**. [b]Isolated yield for both isomers. [c]ee determined by chiral HPLC. [d]*Z*:*E* ratio determined by GC-MS analysis. [e]Sign of specific rotation: + enantiomer or − enantiomer. [f]Reaction conducted in the presence of 2 equiv of $LiClO_4$.

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

Scheme 6. Access to Dipropionate and Deoxypropionate Synthons



apply the new methodology to the asymmetric synthesis of biologically interesting molecules.

EXPERIMENTAL SECTION

General Considerations. THF was freshly distilled from benzophenone ketyl radical under nitrogen prior to use, while Hünig's base (diisopropylethylamine) was distilled from calcium hydride and *N*,*N*-dimethylethylamine was distilled from potassium hydroxide under nitrogen.[26] Most anhydrous solvents (dichloromethane and diethyl ether) were obtained by passing through activated alumina columns on a solvent purification system. Zinc dust (<10 μm), lithium perchlorate, *n*-butyllithium (2.5 M in hexane), $LiAlH_4$ (1.0 M in Et_2O), potassium triethylborohydride (1.0 M in THF), 2-phenylpropanoic acid, 2-phenylbutanoic acid, diphenylacetyl chloride, phenylacetic acid, ethylethynyl ether, and 2-pyridone were purchased and used as received. Propionyl chloride, butyryl chloride, acetoxyacetyl chloride, 4-chlorobutyryl chloride, hexanoyl chloride, octanoyl chloride, valeroyl chloride, and trimethylsilyl chloride were purchased and distilled prior to use.[26] Iatrobeads (neutral silica, 60 μM particle size), and TLC plates (UV254, 250 μM) were used as received. Methylphenylketene, ethylphenylketene, *n*-butylphenylketene, isobutylphenylketene, diphenylketene, dimethylketene, and TMS-ketene were prepared according to literature procedures.[27] TMS-quinine, Me-quinidine, and Me-quinine were synthesized according to literature procedures.[28] (*R*)-Allyl-3-(benzyloxy)-2-(4-methoxybenzylamino)-propanoate (**6**) was synthesized according to a literature procedure.[5]

NMR spectra were recorded on a 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra. High-resolution mass spectra were obtained on an Accurate Mass Q-TOF LC-MS instrument with ESI as the ionization method. Low-resolution mass spectra were recorded on a GC-MS instrument equipped with a mass selective detector and using a GC column (30 m, 0.25 mm i.d.). IR spectra were recorded on an IR spectrometer. Optical rotations were measured on an automatic polarimeter.

Chiral high-performance liquid chromatography analysis (HPLC) was performed using AD, OD-H, OB-H, and AS-H columns (25 × 0.46 cm) on an HPLC instrument attached with diode array detector (deuterium lamp, 190–600 nm) with HPLC-grade isopropyl alcohol and hexanes as the eluting solvents. Enantiomeric excesses were determined at λ 254 or 225 nm (details given for each compound). Chiral gas chromatography analysis (GC) was performed using a Chiraldex B-DM fused silica capillary column (30 m × 0.25 mm × 0.12 μm film thickness) on a gas chromatograph instrument.

Method A for Ketene Heterodimerization. Acyl chloride in dichloromethane was added over the indicated time via syringe pump to a solution of ketene, Hünig's base, and alkaloid catalyst in dichloromethane at −25 °C, and the mixture was stirred for the indicated time.

Method B for Ketene Heterodimerization. Acyl chloride in dichloromethane was added over the indicated time via syringe pump to a solution of ketene, Hünig's base, $LiClO_4$, and alkaloid catalyst in dichloromethane/ether solution at −25 °C, and the mixture was stirred for the indicated time.

Method C for Ketene Heterodimerization (in Situ Generation of both Acceptor and Donor Ketene). Hünig's base was added to a solution of 2-phenylpropionyl chloride or 2-phenylbutyryl chloride in CH_2Cl_2 at the indicated temperature, and the mixture was stirred for the indicated time. The reaction mixture was cooled to −25 °C, Me-quinidine in CH_2Cl_2 was added, and propionyl chloride or butyryl chloride in CH_2Cl_2 was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C.

Previous Compound Characterization. Compounds (+)-**3a**, (−)-**3a**, (+)-**3b**, (−)-**3b**, (+)-**3c**, (−)-**3c**, (+)-**3l**, (−)-**3l**, (+)-**3m**, (−)-**3m**, (+)-**3n**, (−)-**3n**, (+)-(*E*)-**3p**, (−)-(*E*)-**3p**, (+)-(*E*)-**3r**, and (−)-(*E*)-**3r** were fully characterized as previously described.[10] Weinreb amides (+)-**4d**, (−)-**4d**, (+)-**4j**, and (−)-**4j** were obtained from the corresponding ketene heterodimers (**3d**,**j**) through Weinreb amine ring opening, and the amides were fully characterized as previously described.[10] Carboxylic acids (+)-**5g**, (−)-**5g**, (+)-**5h**, (−)-**5h**, (+)-**5i**, and (−)-**5i** were obtained from the corresponding ketene heterodimers (**3g–i**) through Pd/C-catalyzed hydrogenolysis, and the acids were fully characterized as previously described.[20] Compounds (+)-**5a**, (+)-**8d**, and (+)-**9a** were prepared and characterized as previously described.[10,20]

(*R*,*Z*)-3-Ethyl-4-(1-phenylethylidene)oxetan-2-one ((+)-(*Z*)-3e) (Method A). Butyryl chloride (255 mg, 2.39 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methylphenylketene (158 mg, 1.20 mmol), Hünig's base (309 mg, 2.39 mmol), and TMS-quinine (47 mg, 0.12 mmol) in dichloromethane (3.7 mL) at −25 °C. The reaction mixture was stirred at this temperature for another 16 h before being concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (12 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (+)-(*Z*)-**3e** was isolated as a colorless oil (104 mg, 43%), with a *Z*:*E* ratio of >97:3 as determined by GC-MS analysis: HPLC analysis >99% ee (Daicel Chiralcel OB-H column; 1 mL/min; solvent system 10% isopropyl alcohol in hexane; retention times 9.7 min (major)); $[\alpha]_D^{23}$ = +7.6 (*c* = 0.42, CH_2Cl_2); IR (thin film)

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824–7837

2973, 2936, 1705, 1654, 1453, 1377, 1228, 1066, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.56−7.50 (m, 2H), 7.43−7.35 (m, 2H), 7.32−7.25 (m, 1H), 4.30 (dd, J = 7.1, 5.0 Hz, 1H), 2.13−1.93 (m, 2H), 2.03 (s, 3H), 1.15 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 141.4, 136.3, 128.6, 127.4, 127.3, 108.8, 56.7, 20.5, 15.5, 10.3; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{15}O_2)^+$ 203.1072, found 203.1073.

(*S,Z*)-3-Ethyl-4-(1-phenylethylidene)oxetan-2-one ((−)-(*Z*)-3e) (Method A). Butyryl chloride (562 mg, 5.27 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methylphenylketene (348 mg, 2.64 mmol), Hünig's base (945 mg, 5.27 mmol), and Me-quinidine (89 mg, 0.26 mmol) in dichloromethane (9.4 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 2 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (15 g), with 1% EtOAc/hexane (200 mL) and 5% EtOAc/hexane (100 mL) as eluents. The solvent was removed under reduced pressure, and (−)-(*Z*)-**3e** was isolated as a colorless oil (213 mg, 40%)%), with a *Z*:*E* ratio of >97:3 as determined by GC-MS analysis: HPLC analysis >99% ee (Daicel Chiralpak OB-H column; 1 mL/min; solvent system 10% isopropyl alcohol in hexane; retention times 6.4 min (major)], $[\alpha]_D^{23}$ = −5.8 (*c* = 1.24, CH_2Cl_2); IR (thin film) 2973, 2935, 1705, 1657, 1448, 1377, 1067, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.58−7.48 (m, 2H), 7.46−7.33 (m, 2H), 7.32−7.21 (m, 1H), 4.30 (app t, J = 5.4 Hz, 1H), 2.15−1.91 (m, 2H), 2.02 (s, 3H), 1.15 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 141.4, 136.3, 128.6, 127.4, 127.3, 108.8, 56.6, 20.5, 15.5, 10.3; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{15}O_2)^+$ 203.1072, found 203.1070.

(*R,Z*)-3-Ethyl-4-(1-phenylpropylidene)oxetan-2-one ((+)-(*Z*)-3f) (Method A). Butyryl chloride (227 mg, 2.13 mmol) in dichloromethane (0.6 mL) was added over 8 h to a solution of ethylphenylketene (155 mg, 1.06 mmol), Hünig's base (275 mg, 2.13 mmol), and Me-quinine (36 mg, 0.11 mmol) in dichloromethane (1.6 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (14 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (+)-(*Z*)-**3f** was isolated as a colorless oil (167 mg, 73%), with a *Z*:*E* ratio of 91:9 as determined by GC-MS analysis: HPLC analysis 70% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 6.2 min (minor), 10.9 min (major)); $[\alpha]_D^{23}$ = +5.9 (*c* = 0.22, CH_2Cl_2); IR (thin film) 2972, 2939, 1709, 1664, 1455, 1383, 1273, 1224, 1093, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.52−7.45 (m, 1H), 7.45−7.36 (m, 2H), 7.35−7.25 (m, 2H), 4.27 (dd, J = 7.3, 4.8 Hz, 1H), 2.61−2.33 (m, 2H), 2.17−1.92 (m, 2H), 1.18 (t, J = 7.4 Hz, 3H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 141.0, 134.8, 128.5, 128.0, 127.3, 115.7, 56.0, 23.1, 20.5, 13.6, 10.2; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{17}O_2)^+$ 217.1229, found 217.1223.

(*S,Z*)-3-Ethyl-4-(1-phenylpropylidene)oxetan-2-one ((−)-(*Z*)-3f) (Method A). Butyryl chloride (234 mg, 2.20 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of ethylphenylketene (160 mg, 1.10 mmol), Hünig's base (284 mg, 2.20 mmol), and Me-quinidine (37 mg, 0.11 mmol) in dichloromethane (3.4 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After this time the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (14 g), with 1% EtOAc/hexane (200 mL) and 10% EtOAc/hexane (100 mL) as eluents. The solvent was removed under reduced pressure, and (−)-(*Z*)-**3f** was isolated as a colorless oil (154 mg, 65%), with a *Z*:*E* ratio of 87:13 as determined by GC-MS analysis: HPLC analysis 95% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 6.1 min (major), 10.8 min (minor)); $[\alpha]_D^{23}$ = −3.8 (*c* = 0.19, CH_2Cl_2); IR (thin film) 2972, 2938, 1720, 1450, 1383, 1270, 1226, 1106, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.53−7.43 (m, 1H), 7.43−7.33 (m, 2H), 7.33−7.22 (m, 2H), 4.26 (dd, J = 7.0, 4.8 Hz, 1H), 2.60−2.30 (m, 2H), 2.14−1.90 (m, 2H), 1.17 (t, J = 7.4 Hz, 3H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 141.0, 134.8, 128.6, 128.0, 127.4, 115.8, 56.1, 23.2, 20.6, 13.7, 10.3; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{17}O_2)^+$ 217.1229, found 217.1221.

(*R,Z*)-4-(1-Phenylpropylidene)-3-propyloxetan-2-one ((*R,Z*)-3g) (Method A). Valeroyl chloride (230 mg, 1.91 mmol) in dichloromethane (0.9 mL) was added over 8 h to a solution of ethylphenylketene (139 mg, 0.95 mmol), Hünig's base (247 mg, 1.91 mmol), and Me-quinine (33 mg, 0.098 mmol) in dichloromethane (1.1 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (7 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (*R,Z*)-**3g** was isolated as a colorless oil (92% conversion by GC-MS), with a *Z*:*E* ratio of 93:7 as determined by GC-MS analysis: HPLC analysis 72% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.7 min (minor), 10.6 min (major)). (*R,Z*)-**3g** (84 mg) was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (−)-**5g** (56 mg, 61% for two steps), which was fully characterized as previously described.[20]

(*S,Z*)-4-(1-Phenylpropylidene)-3-propyloxetan-2-one ((*S,Z*)-3g) (Method A). Valeroyl chloride (230 mg, 1.91 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of ethylphenylketene (139 mg, 0.95 mmol), Hünig's base (247 mg, 1.91 mmol), and Me-quinidine (33 mg, 0.098 mmol) in dichloromethane (1.0 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (5 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (*S,Z*)-**3g** was isolated as a colorless oil (83% conversion by GC-MS) with a *Z*:*E* ratio of 83:17 as determined by GC-MS analysis: HPLC analysis 95% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.7 min (major), 10.8 min (minor)). (*S,Z*)-**3g** (42 mg) was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (+)-**5g** (19 mg, 37% for 2 steps), which was fully characterized as previously described.[20]

(*R,Z*)-3-Butyl-4-(1-phenylethylidene)oxetan-2-one ((*R,Z*)-3h) (Method A). Hexanoyl chloride (369 mg, 2.74 mmol) in dichloromethane (0.8 mL) was added over 8 h to a solution of methylphenylketene (181 mg, 1.37 mmol), Hünig's base (354 mg, 2.74 mmol), and Me-quinine (46 mg, 0.14 mmol) in dichloromethane (2.1 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (10 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (*R,Z*)-**3h** was isolated as a colorless oil (170 mg, 54%), with a *Z*:*E* ratio of >97:3 as determined by GC-MS analysis: HPLC analysis 74% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.5 min (minor), 8.6 min (major)). (*R,Z*)-**3h** was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (−)-**5h**, which was fully characterized as previously described.[20]

(*R,Z*)-3-Butyl-4-(1-phenylethylidene)oxetan-2-one ((*R,Z*)-3h) (Method A). Hexanoyl chloride (298 mg, 2.21 mmol) in dichloromethane (1.1 mL) was added over 8 h to a solution of methylphenylketene (146 mg, 1.11 mmol), Hünig's base (286 mg, 2.21 mmol), and TMS-quinine (44 mg, 0.11 mmol) in dichloromethane (1.3 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (5 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (*R,Z*)-**3h** was isolated as a colorless oil (142 mg, 55%), with a *Z*:*E* ratio of 97:3 as determined by GC-MS

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

analysis: HPLC analysis 88% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.6 min (minor), 8.7 min (major)). (*R*,*Z*)-**3h** was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (−)-**5h**, which was fully characterized as previously described.[20]

(*S*,*Z*)-3-Butyl-4-(1-phenylethylidene)oxetan-2-one ((*S*,*Z*)-3h) (Method A). Hexanoyl chloride (369 mg, 2.74 mmol) in dichloromethane (0.8 mL) was added over 8 h to a solution of methylphenylketene (181 mg, 1.37 mmol), Hünig's base (354 mg, 2.74 mmol), and Me-quinidine (46 mg, 0.14 mmol) in dichloromethane (2.1 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (5 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (*S*,*Z*)-**3h** was isolated as a colorless oil (202 mg, 64%), with a *Z*:*E* ratio of >97:3 as determined by GC-MS analysis: HPLC analysis 94% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.5 min (major), 8.7 min (minor)). (*S*,*Z*)-**3h** was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (+)-**5h**, which was fully characterized as previously described.[20]

(*R*,*Z*)-3-Butyl-4-(1-phenylpropylidene)oxetan-2-one ((*R*,*Z*)-3i) (Method A). Hexanoyl chloride (301 mg, 2.23 mmol) in dichloromethane (0.9 mL) was added over 8 h to a solution of ethylphenylketene (163 mg, 1.12 mmol), Hünig's base (289 mg, 2.23 mmol), and Me-quinine (38 mg, 0.11 mmol) in dichloromethane (1.4 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (7 g), with 1% EtOAc/hexane (250 mL) as eluent. The solvent was removed under reduced pressure, and (*R*,*Z*)-**3i** was isolated as a colorless oil (95% conversion by GC-MS), with a *Z*:*E* ratio of 93:7 as determined by GC-MS analysis: HPLC analysis 76% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.2 min (minor), 9.5 min (major)). (*R*,*Z*)-**3i** (46 mg) was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (−)-**5i** (25 mg, 51% for two steps), which was fully characterized as previously described.[20]

(*S*,*Z*)-3-Butyl-4-(1-phenylpropylidene)oxetan-2-one ((*S*,*Z*)-3i) (Method A). Hexanoyl chloride (301 mg, 2.23 mmol) in dichloromethane (0.9 mL) was added over 8 h to a solution of ethylphenylketene (163 mg, 1.12 mmol), Hünig's base (289 mg, 2.23 mmol), and Me-quinidine (38 mg, 0.11 mmol) in dichloromethane (1.4 mL) at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction mixture was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (7 g), with hexane (100 mL) and 1% EtOAc/hexane (200 mL) as eluents. The solvent was removed under reduced pressure, and (*S*,*Z*)-**3i** was isolated as a colorless oil (117 mg, 43%), with a *Z*:*E* ratio of 84:16 as determined by GC-MS analysis: HPLC analysis 95% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.1 min (major), 9.5 min (minor)). (*S*,*Z*)-**3i** was subjected to Pd/C-catalyzed hydrogenolysis to provide carboxylic acid (+)-**5i**, which was fully characterized as previously described.[20]

(*S*)-3-Methyl-4-(1-(trimethylsilyl)ethylidene)oxetan-2-one ((+)-3k) (Method B). $LiClO_4$ (42 mg, 0.39 mmol) dissolved in Et_2O (0.4 mL) was added to a solution of TMS-methylketene (100 mg, 0.78 mmol) and Me-quinidine (13 mg, 0.038 mmol) in dichloromethane (0.6 mL) at −25 °C. Hünig's base (51 mg, 0.39 mmol) was then added to the solution. Propionyl chloride (36 mg, 0.39 mmol) in dichloromethane (0.6 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for a further 16 h. The reaction was quenched by the addition of water (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtered solution was concentrated under reduced pressure to about 1 mL. The solution was diluted with pentane (10 mL) and passed through a plug of neutral silica (5 g), with 25% CH_2Cl_2/pentane (200 mL) as eluent. The solvent was removed, and (+)-**3k** was isolated as a colorless liquid (36 mg, 50%), with a *Z*:*E* ratio of 78:22 as determined by GC-MS analysis: $[\alpha]_D^{23}$ = +5.0 (*c* = 0.16, CH_2Cl_2); IR (thin film) 2957, 2925, 2855, 1730, 1600, 1461, 1404, 1379, 1273, 1183, 1122, 1072, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) for major diastereomer δ 4.06 (q, *J* = 7.6 Hz, 1H), 1.67 (s, 3H), 1.51 (d, *J* = 7.6 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer δ 171.2, 151.2, 105.2, 49.5, 13.9, 12.4, −1.2; $(M + H)^+$ HRMS *m*/*z* calcd for $(C_9H_{17}O_2Si)^+$ 185.0998, found 185.0996.

(*R*,*E*)-3-Methyl-4-(1-phenylpentylidene)oxetan-2-one ((+)-(*E*)-3q) (Method B). $LiClO_4$ (85 mg, 0.80 mmol) dissolved in Et_2O (0.8 mL) was added to a solution of *n*-butylphenylketene (139 mg, 0.80 mmol) and TMS-quinine (32 mg, 0.08 mmol) in dichloromethane (0.8 mL) at −25 °C. Hünig's base (207 mg, 1.60 mmol) was then added to the solution. Propionyl chloride (148 mg, 1.60 mmol) in dichloromethane (0.9 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for another 16 h. The reaction was quenched by the addition of water (20 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtered solution was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (5 g), with hexane (50 mL) and then 1% EtOAc/hexane (200 mL) as eluents. The solvent was removed under reduced pressure, and (+)-(*E*)-**3q** was isolated as a colorless oil (127 mg, 69%), with a *Z*:*E* ratio of 24:76 as determined by GC-MS analysis: HPLC analysis 84% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 6.9 min (minor), 11.7 min (major)); $[\alpha]_D^{23}$ = +5.9 (*c* = 0.16, CH_2Cl_2); IR (thin film) 2957, 2931, 2872, 1709, 1600, 1495, 1448, 1378, 1290, 1203, 1181, 1062, 1041, 922, 868, 770, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) for major diastereomer δ 7.43−7.30 (m, 2H), 7.30−7.19 (m, 3H), 4.21 (q, *J* = 7.6 Hz, 1H), 2.67−2.52 (m, 1H), 2.52−2.40 (m, 1H), 1.46−1.20 (m, 4H), 1.16 (d, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer δ 170.5, 144.1, 136.6, 128.8, 127.9, 127.5, 116.3, 49.1, 30.1, 29.1, 22.5, 14.0, 11.7; $(M + H)^+$ HRMS *m*/*z* calcd for $(C_{15}H_{19}O_2)^+$: 231.1385, found 231.1382.

(*S*,*E*)-3-Methyl-4-(1-phenylpentylidene)oxetan-2-one ((−)-(*E*)-3q) (Method B). $LiClO_4$ (92 mg, 0.86 mmol) dissolved in Et_2O (0.9 mL) was added to a solution of *n*-butylphenylketene (150 mg, 0.86 mmol) and Me-quinidine (29 mg, 0.086 mmol) in dichloromethane (0.9 mL) at −25 °C. Hünig's base (224 mg, 1.73 mmol) was then added to the solution. Propionyl chloride (160 mg, 1.73 mmol) in dichloromethane (1.1 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction was quenched by the addition of water (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the reaction was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (5 g), eluting with hexane (50 mL), and then 1% EtOAc/hexane (200 mL). The solvent was removed under reduced pressure and (−)-*E*-**3q** was isolated as a colorless oil (154 mg, 78%), with a *Z*:*E* ratio of 26:74 as determined by GC-MS analysis: HPLC analysis 92% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 7.4 min (major), 13.1 min (minor)); $[\alpha]_D^{23}$ = −3.1 (*c* = 0.16, CH_2Cl_2); IR (thin film) 2957, 2931, 2872, 1714, 1600, 1496, 1449, 1379, 1256, 1211, 1185, 1126, 1071, 1025, 922, 868, 770, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) for major diastereomer δ 7.42−7.31 (m, 2H), 7.31−7.20 (m, 3H), 4.21 (q, *J* = 7.6 Hz, 1H), 2.66−2.53 (m, 1H), 2.53−2.41 (m, 1H), 1.46−1.20 (m, 4H), 1.16 (d, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer δ 170.5, 144.1,

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

136.6, 128.8, 127.9, 127.5, 116.3, 49.1, 30.1, 29.1, 22.5, 14.0, 11.7; (M + H)$^+$ HRMS m/z calcd for $(C_{15}H_{19}O_2)^+$ 231.1385, found 231.1384.

(*R*,*E*)-3-Ethyl-4-(1-phenylpropylidene)oxetan-2-one ((+)-(*E*)-3s) (Method B). $LiClO_4$ (361 mg, 3.40 mmol) dissolved in Et_2O (1.6 mL) was added to a solution of ethylphenylketene (248 mg, 1.70 mmol) and TMS-quinine (67 mg, 0.17 mmol) in dichloromethane (2.2 mL) at −25 °C. Hünig's base (349 mg, 3.40 mmol) was then added to the solution. Butyryl chloride (362 mg, 3.40 mmol) in dichloromethane (1.0 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for a further 16 h. The reaction was quenched by the addition of water (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtered solution was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (10 g), with 1% EtOAc/hexane (250 mL) as eluent. The solvent was removed under reduced pressure, and (*R*,*E*)-**3s** was isolated as a colorless oil (315 mg, 86%), with a *Z*:*E* ratio of 26:74 as determined by GC-MS analysis: HPLC analysis 93% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 4.7 min (minor), 5.1 min (major)); $[\alpha]_D^{23}$ = +7.8 (c = 1.58, CH_2Cl_2); IR (thin film) 2968, 2935, 1704, 1494, 1385, 1275, 1178, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) for major diastereomer δ 7.42−7.34 (m, 2H), 7.33−7.23 (m, 3H), 4.26 (dd, J = 6.9, 4.4 Hz, 1H), 2.73−2.60 (m, 1H), 2.59−2.44 (m, 1H), 1.71−1.57 (m, 1H), 1.57−1.42 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer δ 169.9, 141.8, 136.4, 128.8, 127.7, 127.5, 118.1, 55.5, 22.8, 19.4, 13.0, 10.1; (M + H)$^+$ HRMS m/z calcd for $(C_{14}H_{17}O_2)^+$ 217.1229, found 217.1226.

(*S*,*E*)-3-Ethyl-4-(1-phenylpropylidene)oxetan-2-one ((−)-(*E*)-3s) (Method B). $LiClO_4$ (361 mg, 3.40 mmol) dissolved in Et_2O (1.6 mL) was added to a solution of ethylphenylketene (248 mg, 1.70 mmol) and Me-quinidine (57 mg, 0.17 mmol) in dichloromethane (2.2 mL) at −25 °C. Hünig's base (349 mg, 3.40 mmol) was then added to the solution. Butyryl chloride (362 mg, 3.40 mmol) in dichloromethane (1.0 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction was quenched by the addition of water (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtered solution was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (10 g), with 1% EtOAc/hexane (250 mL) as eluent. The solvent was removed under reduced pressure, and (−)-(*E*)-**3s** was isolated as a colorless oil (315 mg, 86%), with a *Z*:*E* ratio of 24:76 as determined by GC-MS analysis: HPLC analysis 88% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.1 min (minor), 4.7 min (major)); $[\alpha]_D^{23}$ = −5.7 (c = 0.60, CH_2Cl_2); IR (thin film) 2968, 2930, 1701, 1494, 1382, 1274, 1174, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) for major diastereomer δ 7.42−7.34 (m, 2H), 7.33−7.22 (m, 3H), 4.26 (dd, J = 6.7, 4.9 Hz, 1H), 2.73−2.60 (m, 1H), 2.58−2.45 (m, 1H), 1.70−1.57 (m, 1H), 1.56−1.43 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer δ 169.9, 141.8, 136.4, 128.8, 127.7, 127.5, 118.1, 55.5, 22.8, 19.4, 13.0, 10.1; (M + H)$^+$ HRMS m/z calcd for $(C_{14}H_{17}O_2)^+$ 217.1229, found 217.1225.

(*R*,*E*)-3-Ethyl-4-(3-methyl-1-phenylbutylidene)oxetan-2-one ((−)-(*E*)-3t) (Method B). $LiClO_4$ (133 mg, 1.25 mmol) dissolved in Et_2O (1.3 mL) was added to a solution of isobutylphenylketene (217 mg, 1.25 mmol) and TMS-quinine (50 mg, 0.13 mmol) in dichloromethane (1.9 mL) at −25 °C. Hünig's base (323 mg, 2.50 mmol) was then added to the solution. Butyryl chloride (266 mg, 2.50 mmol) in dichloromethane (0.6 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for another 16 h. The reaction was quenched by the addition of water (20 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtered solution was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (15 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (−)-(*E*)-**3t** was isolated as a colorless oil (231 mg, 76%), with a *Z*:*E* ratio of 6:94 as determined by GC-MS analysis: HPLC analysis 97% ee (Daicel Chiralpak AS-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 3.8 min (minor), 5.7 min (major)); $[\alpha]_D^{23}$ = −6.0 (c = 0.10, CH_2Cl_2); IR (thin film) 2958, 2935, 1706, 1600, 1495, 1386, 1283, 1178, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.41−7.33 (m, 2H), 7.33−7.28 (m, 1H), 7.28−7.22 (m, 2H), 4.26 (dd, J = 7.1, 5.0 Hz, 1H), 2.45 (d, J = 7.4 Hz, 2H), 1.74−1.55 (m, 2H), 1.55−1.40 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 142.7, 136.9, 128.8, 127.8, 127.5, 116.0, 55.4, 38.4, 26.8, 23.0, 21.9, 19.5, 10.1; (M + H)$^+$ HRMS m/z calcd for $(C_{16}H_{21}O_2)^+$ 245.1542, found 245.1538.

(*S*,*E*)-3-Ethyl-4-(3-methyl-1-phenylbutylidene)oxetan-2-one ((+)-(*E*)-3t) (Method B). $LiClO_4$ (133 mg, 1.25 mmol) dissolved in Et_2O (1.3 mL) was added to a solution of isobutylphenylketene (217 mg, 1.25 mmol) and Me-quinidine (43 mg, 0.13 mmol) in dichloromethane (1.9 mL) at −25 °C. Hünig's base (323 mg, 2.50 mmol) was then added to the solution. Butyryl chloride (266 mg, 2.50 mmol) in dichloromethane (0.6 mL) was added over 8 h to the above solution at −25 °C, and the mixture was stirred at this temperature for another 16 h. After 16 h the reaction was quenched by the addition of water (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the filtered solution was concentrated under reduced pressure to about 1 mL. The solution was diluted with 1% EtOAc/hexane (10 mL) and passed through a plug of neutral silica (15 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (+)-(*E*)-**3t** was isolated as a colorless oil (268 mg, 88%), with a *Z*:*E* ratio of 5:95 as determined by GC-MS analysis: HPLC analysis 98% ee (Daicel Chiralpak AS-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 5.6 min (minor), 3.8 min (major)); $[\alpha]_D^{23}$ = +33.5 (c = 0.50, CH_2Cl_2); IR (thin film) 2968, 2935, 1703, 1600, 1495, 1382, 1272, 1183, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.41−7.33 (m, 2H), 7.33−7.28 (m, 1H), 7.28−7.21 (m, 2H), 4.27 (*app* t, J = 5.2 Hz, 1H), 2.45 (d, J = 7.3 Hz, 2H), 1.74−1.54 (m, 2H), 1.54−1.41 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 142.7, 136.9, 128.8, 127.8, 127.5, 116.1, 55.4, 38.5, 26.8, 23.0, 22.0, 19.6, 10.1; (M + H)$^+$ HRMS m/z calcd for $(C_{16}H_{21}O_2)^+$: 245.1542, found 245.1540.

Formation of (−)-3a through in Situ Generation of both Acceptor and Donor Ketene with 2.5 mol % Catalyst Loading (Method C). Hünig's base (593 mg, 4.59 mmol) was added to a solution of 2-phenylpropionyl chloride (257 mg, 1.53 mmol) in CH_2Cl_2 (4.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then the reaction mixture was cooled to −25 °C. Me-quinidine (13 mg, 0.038 mmol) in CH_2Cl_2 (0.9 mL) was then added to the reaction mixture, followed by propionyl chloride (283 mg, 3.06 mmol) in CH_2Cl_2 (0.9 mL), which was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C and then was quenched by adding deionized water (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and the filtered solution was concentrated under reduced pressure to about 3 mL. The solution was diluted with 1% EtOAc/hexane (15 mL) and passed through a plug of neutral silica (6 g), with hexane (50 mL) and 1% EtOAc/hexane (200 mL) as eluents. The solvent was removed under reduced pressure, and (−)-**3a** was isolated as a colorless oil (212 mg, 74%), with a *Z*:*E* ratio of 99:1 as determined by GC-MS analysis: HPLC analysis 92% ee (Daicel Chiralpak OB-H column; 1 mL/min; solvent system 10% isopropyl alcohol in hexane; retention times 9.1 min (major), 16.3 min

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

(minor)); $[\alpha]_D^{23}$ = −20.2 (*c* = 0.042, CH_2Cl_2); NMR spectra matched those of (−)-**3a** previously described.[10]

Formation of (+)-3a through in Situ Generation of both Acceptor and Donor Ketene (Method C). Hünig's base (1527 mg, 11.82 mmol) was added to a solution of 2-phenylpropionyl chloride (662 mg, 3.94 mmol) in CH_2Cl_2 (10.8 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then the reaction mixture was cooled to −25 °C. TMS-quinine (156 mg, 0.39 mmol) in CH_2Cl_2 (4.2 mL) was then added to the reaction mixture, followed by propionyl chloride (729 mg, 7.88 mmol) in CH_2Cl_2 (0.6 mL), which was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C and then was quenched by adding deionized water (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and the filtered solution was concentrated under reduced pressure to about 3 mL. The solution was diluted with 1% EtOAc/hexane (15 mL) and passed through a plug of neutral silica (16 g), with 1% EtOAc/hexane (500 mL) as eluent. The solvent was removed under reduced pressure, and (+)-**3a** was isolated as a colorless oil (496 mg, 67%), with a *Z*:*E* ratio of 99:1 as determined by GC-MS analysis: HPLC analysis 93% ee (Daicel Chiralpak OB-H column; 1 mL/min; solvent system 10% isopropyl alcohol in hexane; retention times 9.3 min (minor), 15.7 min (major)); $[\alpha]_D^{23}$ = +18.0 (*c* = 0.064, CH_2Cl_2); NMR spectra matched those of (+)-**3a** previously reported.[10]

Formation of (−)-3b through in Situ Generation of both Acceptor and Donor Ketene (Method C). Hünig's base (360 mg, 2.79 mmol) was added to a solution of 2-phenylbutanoyl chloride (169 mg, 0.93 mmol) in CH_2Cl_2 (2.5 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then the reaction mixture was cooled to −25 °C. Me-quinidine (31 mg, 0.092 mmol) in CH_2Cl_2 (0.4 mL) was then added to the reaction mixture, followed by propionyl chloride (172 mg, 1.86 mmol) in CH_2Cl_2 (0.8 mL), which was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C and then was quenched by adding deionized water (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and the filtered solution was concentrated under reduced pressure to about 3 mL. The solution was diluted with 1% EtOAc/hexane (15 mL) and passed through a plug of neutral silica (5 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (−)-**3b** was isolated as a colorless oil (90 mg, 48%), with a *Z*:*E* ratio of 78:22 as determined by GC-MS analysis: HPLC analysis 95% ee (Daicel Chiralpak OB-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 10.6 min (major), 23.3 min (minor)); $[\alpha]_D^{23}$ = −12.1 (*c* = 0.26, CH_2Cl_2); NMR spectra matched those of (−)-**3b** as previously described.[10]

Formation of (−)-3e through in Situ Generation of both Acceptor and Donor Ketene (Method C). Hünig's base (307 mg, 2.38 mmol) was added to a solution of 2-phenylpropionyl chloride (133 mg, 0.79 mmol) in CH_2Cl_2 (2.1 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature, and then the reaction mixture was cooled to −25 °C. Me-quinidine (27 mg, 0.08 mmol) in CH_2Cl_2 (0.3 mL) was then added to the reaction mixture, followed by butyryl chloride (169 mg, 1.59 mmol) in CH_2Cl_2 (0.8 mL), which was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C and then was quenched by adding deionized water (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and the filtered solution was concentrated under reduced pressure to about 3 mL. The solution was diluted with 1% EtOAc/hexane (15 mL) and passed through a plug of neutral silica (5 g), with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (−)-**3e** was isolated as a colorless oil (113 mg, 71%), with a *Z*:*E* ratio of 98:2 as determined by GC-MS analysis: HPLC analysis 97% ee (Daicel Chiralpak OB-H column; 1 mL/min; solvent system 10% isopropyl alcohol in hexane; retention times 6.4 min (major), 9.9 min (minor)); $[\alpha]_D^{23}$ = −7.9 (*c* = 1.02, CH_2Cl_2); NMR spectra matched those of (−)-**3e** previously prepared.[10]

Formation of (−)-3f through in Situ Generation of Both Acceptor and Donor Ketene (Method C). Hünig's base (354 mg, 2.74 mmol) was added to a solution of 2-phenylbutanoyl chloride (166 mg, 0.91 mmol) in CH_2Cl_2 (2.5 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then the reaction mixture was cooled to −25 °C. Me-quinidine (31 mg, 0.092 mmol) in CH_2Cl_2 (0.4 mL) was then added to the reaction mixture, followed by butyryl chloride (194 mg, 1.82 mmol) in CH_2Cl_2 (0.8 mL), which was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C and then was quenched by adding deionized water (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and the filtered solution was concentrated under reduced pressure to about 3 mL. The solution was diluted with 1% EtOAc/hexane (15 mL) and passed through a plug of neutral silica (5 g) with 1% EtOAc/hexane (300 mL) as eluent. The solvent was removed under reduced pressure, and (−)-**3f** was isolated as a colorless oil (69 mg, 35%), with a *Z*:*E* ratio of 86:14 as determined by GC-MS analysis: HPLC analysis 97% ee (Daicel Chiralpak OD-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 6.0 min (major), 10.4 min (minor)); $[\alpha]_D^{23}$ = −3.4 (*c* = 1.32, CH_2Cl_2); NMR spectra matched those of (−)-**3f** previously prepared.[10]

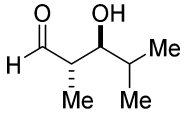
Formation of (*S*,*E*)-(*E*)-3p through in Situ Generation of Both Acceptor and Donor Ketene (Method C). Hünig's base (309 mg, 3.94 mmol) was added to a solution of 2-phenylbutanoyl chloride (239 mg, 1.31 mmol) in CH_2Cl_2 (3.7 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then the reaction mixture was cooled to −25 °C. Me-quinidine (44 mg, 0.13 mmol) in CH_2Cl_2 (0.8 mL) and $LiClO_4$ (279 mg, 2.62 mmol) in Et_2O (2.6 mL) were then added to the reaction mixture, followed by propionyl chloride (243 mg, 2.63 mmol) in CH_2Cl_2 (0.8 mL), which was added over 8 h via syringe pump. The reaction mixture was stirred for 12 h at −25 °C and then was quenched by adding deionized water (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organics were dried over anhydrous sodium sulfate, and the filtered solution was concentrated under reduced pressure to about 3 mL. The solution was diluted with 1% EtOAc/hexane (15 mL) and passed through a plug of neutral silica (9 g), with hexane (50 mL) and 1% EtOAc/hexane (300 mL) as eluents. The solvent was removed under reduced pressure, and (−)-*E*-**3p** was isolated as a colorless oil (109 mg, 41%), with a *Z*:*E* ratio of 33:67 as determined by GC-MS analysis: HPLC analysis >99% ee (Daicel Chiralpak OB-H column; 1 mL/min; solvent system 2% isopropyl alcohol in hexane; retention times 6.3 min (major))); NMR spectra matched those of (−)-*E*-**3p** previously prepared.[10]

(*R*)-Allyl 2-((*R*)-2-Acetyl-*N*-(4-methoxybenzyl)octanamido)-3-(benzyloxy)propanoate ((+)-7). (−)-**3n** (28 mg, 0.12 mmol), serine derivative **6**[5] (82 mg, 0.23 mmol), and 2-pyridone (23 mg, 0.24 mmol) were dissolved in THF (0.6 mL) and stirred at 50 °C for 55 h. After this time, the reaction mixture was cooled to room temperature, TBAF (0.23 mL, 0.23 mmol, 1 M solution in THF) was added, and the reaction mixture was stirred for 10 min before water (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude was purified by column chromatography with gradient elution (10−15% EtOAc/Hexane) to afford (+)-7 as a colorless oil (50 mg, 82%) with dr 3:1 as determined by ^1H NMR (diastereomers are separable by column chromatography): $[\alpha]_D^{23}$ = +25.5 (*c* = 0.09, CH_2Cl_2) for a diastereomerically enriched sample (dr 9:1); IR (thin film) 2165, 1737, 1645 cm^{-1}; ^1H NMR for the major diastereomer (400 MHz, $CDCl_3$, TMS) δ 7.34−7.14 (m, 9H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.93−5.83 (m, 1H), 5.33−5.22 (m, 2H), 4.83 (d, *J* = 17.2 Hz, 1H), 4.66−4.54 (m, 4H), 4.40 (d, *J* = 3.2 Hz, 2H), 4.04−3.92 (m, 2H), 3.80 (s, 3H), 3.51 (dd, *J* = 5.6, 8.0 Hz, 1H), 2.12 (s, 3H), 2.03−2.91 (m, 1H), 1.72−1.65 (m, 1H), 1.35−1.24 (m, 6H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the major

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

diastereomer δ 205.3, 170.7, 168.7, 159.4, 137.9, 132.0, 128.9, 128.6, 128.3, 127.9, 127.8, 118.9, 114.3, 73.6, 68.7, 66.2, 59.9, 59.0, 55.5, 51.8, 31.7, 29.8, 29.2, 27.7, 27.1, 22.8, 14.2; $(M + H)^+$ HRMS m/z calcd for $(C_{31}H_{42}NO_6)^+$ 524.3007, found 524.3003.

Stererochemical Proofs. *Absolute and Relative Stereochemistry.*

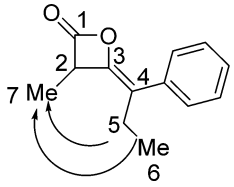


(*S,S*)-*anti*-10

(+)-**8d** (derived from (−)-**4d**) was converted to aldol product **10**, through treatment with $LiAlH_4$ (1.0 M in Et_2O, 2 equiv) in THF (0.2 M) at −78 °C for 80 min, a compound whose data were in agreement with the ^1H NMR data previously reported for the aldol product possessing anti relative stereochemistry.[29a]

The specific rotation value measured for **10** was in good agreement with that reported for the (*S,S*)-*anti*-aldol product reported by MacMillan and co-workers, and hence heterodimer **3d** derived Weinreb amide (−)-**4d** was assigned the *S* configuration.[29b] By analogy, all heterodimers formed through Me-quinidine catalysis were assigned the *S* configuration, while all heterodimers formed through Me-quinine or TMS-quinine catalysis were assigned the *R* configuration.

Olefin Geometry Determination.



The *Z* configuration of (*S,Z*)-**3b** was determined by the NOEs between C5−C7 and C6−C7, in comparison with (*S,E*)-**3b**. The olefin geometry for all the other heterodimers was assigned by analogy.

General Computational Methods (see the Supporting Information for details). Data were calculated at the B3LYP/6-31+G(d,p) level of theory using Gaussian 09 for all compounds with Gabedit to generate inputs (modified manually as necessary), Avogadro to visualize output, and images generated using ORTEP. Solvent was accounted for using the integral equation formalism for polarizable continuum model (IEFPCM) as implemented by Gaussian using the SCRF = (Solvent = Dichloromethane) command where ε = 8.93. Temperature was accounted for using Temperature = 248.15. Transition states were verified by vibrational frequency analysis to find only one negative frequency corresponding to the appropriate bond formation as visualized with Avogadro.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01481.

Spectroscopic data and chromatograms for all new compounds (PDF)

Computational data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for N.J.K.: kerrigan@oakland.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support has been provided by the National Science Foundation and the National Institutes of Health: Grant Nos. CHE-1213638, CHE-1463728, and R15GM107800 to N.J.K., CHE-0821487 for NMR facilities at Oakland University, and CHE-1048719 for LC-MS facilities at Oakland University.

■ REFERENCES

(1) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444−2448.

(2) England, D. C.; Krespan, C. G. *J. Org. Chem.* **1970**, *35*, 3322−3327.

(3) Brady, W. T.; Ting, P. L. *J. Org. Chem.* **1975**, *40*, 3417−3420.

(4) (a) Moore, H. W.; Wilbur, D. S. *J. Org. Chem.* **1980**, *45*, 4483−4491. (b) Moore, H. W.; Wilbur, D. S. *J. Am. Chem. Soc.* **1978**, *100*, 6523−6525.

(5) (a) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143−2146. (b) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803−4805.

(6) Marqués-López, E.; Christmann, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8696−8698.

(7) For reviews covering the asymmetric synthesis of β-lactones from ketenes see: (a) Chen, S.; Salo, E. C.; Kerrigan, N. J. In *Science of Synthesis Reference Library, Asymmetric Organocatalysis*; List, B., Ed.; Thieme: Stuttgart, Germany, 2012; Vol. *1* (Lewis Base and Acid Catalysts), Chapter 1.1.10, pp 455−496. (b) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771−6803. (c) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565. (d) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403−6434.

(8) For applications of enantioenriched β-lactones in synthesis see: (a) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412−10422. (b) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470−10471. (c) Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500−7504. (d) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127−13129. (e) Calter, M. A.; Song, W.; Zhou, J. *J. Org. Chem.* **2004**, *69*, 1270−1275. (f) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654−13655. (g) Romo, D.; Wang, Y.; Tennyson, R. L. *Heterocycles* **2004**, *64*, 605−658. (h) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438−7439. (i) Duffy, R. J.; Morris, K. A.; Vallakati, R.; Zhang, W.; Romo, D. *J. Org. Chem.* **2009**, *74*, 4772−4781.

(9) For examples of β-lactones as integral features of biologically active molecules see: (a) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, *1995*, 729−744. (b) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4−5. (c) Dymock, B. W.; Kocienski, P. J.; Pons, J.-M. *Synthesis* **1998**, *1998*, 1655−1661. (d) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230−6231. (e) Yin, J.; Yang, X. B.; Chen, Z. X.; Zhang, Y. H. *Chin. Chem. Lett.* **2005**, *16*, 1448−1450. (f) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497−4500. (g) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143−2146. (h) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803−4805.

(10) Ibrahim, A. A.; Nalla, D.; Van Raaphorst, M.; Kerrigan, N. J. *J. Am. Chem. Soc.* **2012**, *134*, 2942−2945.

(11) (a) Ibrahim, A. A.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2009**, *74*, 1777−1780. (b) Ibrahim, A. A.; Wei, P.-H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901−7904. (c) Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2010**, *12*, 1664−1667. (d) Wei, P.-H.; Ibrahim, A. A.; Mondal, M.; Nalla, D.; Harzmann, G. D.; Tedeschi, F. A.; Wheeler, K. A.; Kerrigan, N. J. *Tetrahedron Lett.* **2010**, *51*, 6690−6694. (e) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784−1787. (f) Chen, S.; Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. *J. Org. Chem.* **2014**, *79*, 4920−4929. (g) Mondal, M.; Chen, S.; Othman, N.; Wheeler, K. A.; Kerrigan, N. J. *J. Org. Chem.* **2015**, *80*, 5789−5794. (h) Chen, S.; Mondal, M.; Adams, M. P.; Wheeler, K. A.; Kerrigan, N. J. *Tetrahedron Lett.* **2015**, *56*, 6421−6424.

(12) (a) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006−8007. (b) Calter, M. A.; Orr, R. K. *Org. Lett.* **2003**, *5*, 4745−4748. (c) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549−4558.

(13) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635.

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837

(14) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 828−831.
(15) (a) Bassindale, A. R.; Taylor, P. G. In *The chemistry of organic silicon compounds*; Patai, S., Rappoport, Z.. Eds.; Wiley: New York, 1989; pp 893−963. (b) Wetzel, D. M.; Brauman, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8333−8336.
(16) Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002**, *58*, 8351−8356.
(17) For related computational studies of nucleophile-catalyzed reactions, see: (a) Zhang, M.; Wei, D.; Wang, Y.; Li, S.; Liu, J.; Zhu, Y.; Tang, M. *Org. Biomol. Chem.* **2014**, *12*, 6374−6383. (b) Johnston, R. C.; Cohen, D. T.; Eichman, C. C.; Scheidt, K. A. *Chem. Sci.* **2014**, *5*, 1974−1982.
(18) (a) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 1754−1756. (b) Seidl, E. T.; Schaefer, H. F. *J. Am. Chem. Soc.* **1991**, *113*, 5195−5200.
(19) Fox, J. M.; Dmitrenko, O.; Liao, L.-a.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317−7328.
(20) Chen, S.; Ibrahim, A. A.; Mondal, M.; Magee, A. J.; Cruz, A. J.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2015**, *17*, 3248−3251.
(21) Olefin geometry was assigned on the basis of NOE experiments. See ref 10 for more details.
(22) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308−5309.
(23) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281−1290.
(24) Wojtovich, A. P.; Brookes, P. S. *Basic Res. Cardiol.* **2009**, *104*, 121−129.
(25) Gaunt, M. J.; Johansson, C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8−27.
(26) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: London, 2002.
(27) (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006. (b) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176. (c) Allen, A. D.; Baigrie, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138. (d) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358. (e) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607.
(28) (a) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 828−831. (b) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006.
(29) (a) Mahrwald, R.; Costisella, B.; Guendogan, B. *Synthesis* **1998**, *1998*, 262. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

DOI: 10.1021/acs.joc.6b01481
J. Org. Chem. 2016, 81, 7824−7837