DOI: 10.1002/chem.201003383

Enantioselective Decarboxylative Alkylation Reactions: Catalyst Development, Substrate Scope, and Mechanistic Studies

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Abstract: α-Quaternary ketones are accessed through novel enantioselective alkylations of allyl and propargyl electrophiles by unstabilized prochiral enolate nucleophiles in the presence of palladium complexes with various phosphinooxazoline (PHOX) ligands. Excellent yields and high enantiomeric excesses are obtained from three classes of enolate precursor: enol carbonates, enol silanes, and racemic β-ketoesters. Each of these substrate classes functions with nearly identical efficiency in terms of yield and enantioselectivity. Catalyst discovery and development, the optimization of reaction conditions, the exploration of reaction scope, and applications in target-directed synthesis are reported. Experimental observations suggest that these alkylation reactions occur through an unusual inner-sphere mechanism involving binding of the prochiral enolate nucleophile directly to the palladium center.

Keywords: alkylation · allylic compounds · asymmetric catalysis · enolates · reaction mechanisms · synthetic methods

Introduction

The catalytic asymmetric synthesis of all-carbon quaternary stereocenters remains a significant challenge in synthetic chemistry.[1] Despite the demanding steric requirements of quaternary stereocenter formation, a number of useful catalytic transformations, including Diels–Alder,[2] Heck,[3] cyclopropanation,[4] alkylation,[5] acylation,[6] desymmetrization,[7] and pericyclic[8] reactions, among others, have been successful in generating these moieties. Although palladium-catalyzed enantioselective allylic alkylation chemistry has been an important tool in organic synthesis, only relatively recently has palladium(II) π-allyl chemistry been used for the formation of quaternary stereocenters.[9] The vast majority of palladium-catalyzed C–C bond-forming allylic alkylations studied by the groups of Trost, Helmchen, Pfaltz, and others form tertiary stereocenters by the attack of stabilized anions (e.g., malonate) on prochiral 1,3-disubstituted allyl fragments.[9] Helmchen and co-workers have shown that reactions with palladium phosphinooxazoline (PHOX) complexes typically occur through outer-sphere malonate attack at the allyl terminus.[10] Although allylic alkylation mediated by other metals, especially copper,[11] has successfully generated quaternary centers on prochiral allyl groups, to our knowledge, this mode of reactivity has not been realized with palladium.[12]

An alternative, less common strategy in allylic alkylation is the use of prochiral nucleophiles. A quaternary stereocenter may be formed on a prochiral nucleophile if it possesses three distinct substituents. These reactions require a remote chiral ligand to discriminate between the prochiral faces of an incoming nucleophile, and thus may seem a more challenging strategy. However, the groups of Hayashi,[13] Ito,[14] and Trost[15] have reported the asymmetric allylation of prochiral enolates derived from 1,3-dicarbonyl compounds. Trost and co-workers have demonstrated that diamine-derived ligands **6** and **7**, which were designed to project bulk in front of the allyl fragment due to their large bite angles, are able to favor one face of the in situ generated ketone enolate (Scheme 1).[5,16,17,18] These reactions represented a significant advance in asymmetric allylation technology by forming quaternary stereocenters in excellent yield and good *ee*. However, the substrate scope of these reactions was restricted to ketone substrates containing either a single

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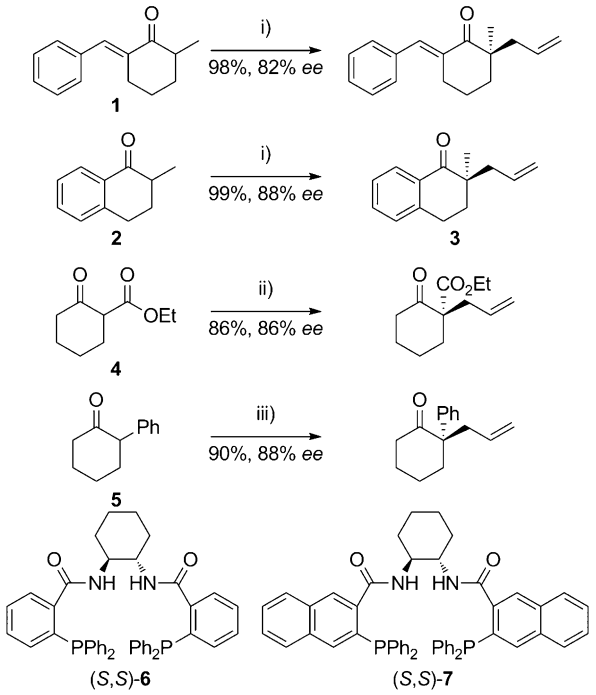
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003383.

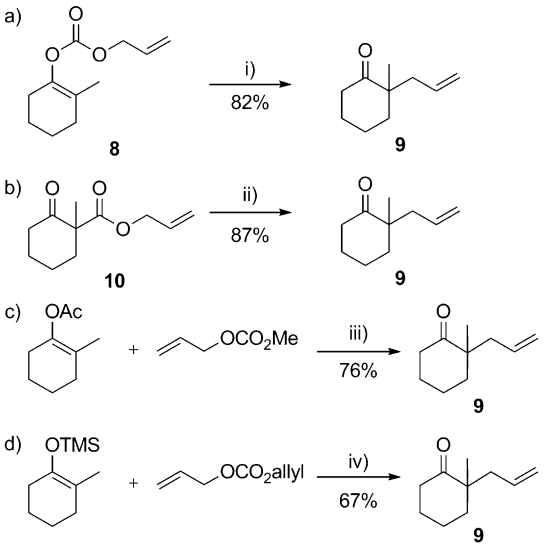


Scheme 1. Trost's allylic alkylation with prochiral nucleophiles. i) (*S*,*S*)-**6**, [{(η^3-C_3H_5)PdCl}$_2$], lithium diisopropylamide (LDA), Me_3SnCl, C_3H_5OAc, dimethoxyethane (DME); ii) (*R*,*R*)-**6**, [{(η^3-C_3H_5)PdCl}$_2$], tetramethylguanidine (TMG), C_3H_5OAc, toluene; iii) (*S*,*S*)-**7**, [{(η^3-C_3H_5)PdCl}$_2$], sodium hexamethyldisilazide (NaHMDS), C_3H_5OAc, DME.

acidic site (e.g., ketone **1** and tetralone **2**) or two α-sites that have a large difference in acidity (e.g., β-ketoester **4** and α-phenyl ketone **5**).[1d] These limitations have prevented direct access to fundamental α-quaternary ketones, such as 2-allyl-2-methylcyclohexanone (**9**), a cyclohexanone derivative not known as a single enantiomer prior to our work.[19]

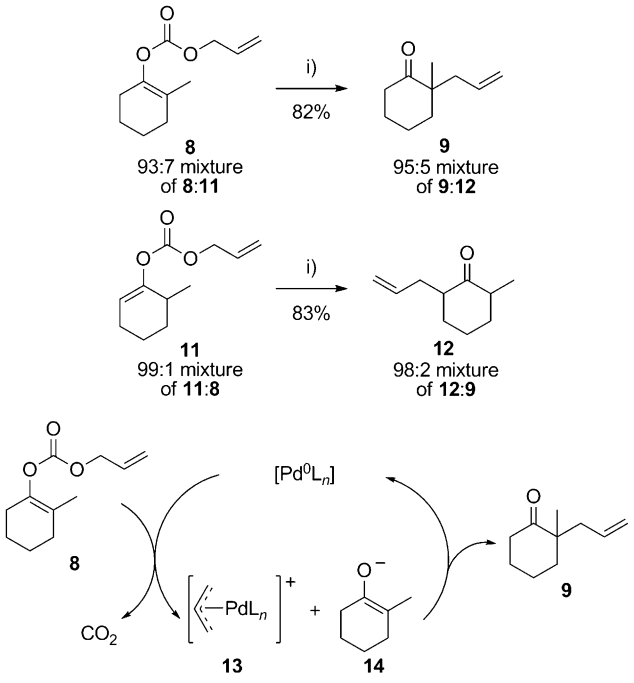
We were confronted by these limitations during studies towards the synthesis of several natural products.[20] A survey of the literature revealed that the non-enantioselective alkylation reactions developed by Tsuji and co-workers[21] in the early 1980s had the proper reactivity and selectivity to form quaternary stereocenters in the presence of less substituted ketone α-sites of similar acidity. For example, allyl enol carbonate and allyl β-ketoester substrates contain both a latent enolate and an allyl fragment (Scheme 2a and b).[21] Alternatively, enol acetates and silyl enol ethers may serve as enolate precursors in intermolecular reactions with allyl carbonates (Scheme 2c and d).[22] These alkylations have the advantage that the reaction occurs under nearly neutral conditions and often at mild temperatures. Despite their advantages, these alkylation reactions were rarely utilized during the twenty years between 1983 and the time we began research in 2003.[23,24]

Our analysis of Tsuji's alkylation reaction showed it to be an ideal candidate for asymmetric catalysis. These high-yielding alkylation methods are a clear case of ligand-accelerated catalysis, occurring only in the presence of phosphine



Scheme 2. Tsuji's allylation methods. i) [$Pd_2(dba)_3$] (dba = dibenzylideneacetone), Ph_3P, dioxane, 0 °C; ii) [$Pd_2(dba)_3$], Ph_3P, THF; iii) [$Pd_2(dba)_3$], 1,2-bis(diphenylphosphino)ethane (DPPE), $MeOSnBu_3$, dioxane, reflux; iv) [$Pd_2(dba)_3$], DPPE, THF (TMS = trimethylsilyl).

ligands.[25] Of additional interest was the regiochemical fidelity observed in the alkylation reactions (Scheme 3). Tsuji and co-workers demonstrated that both tetrasubstituted allyl enol carbonate isomer **8** and trisubstituted allyl enol carbonate isomer **11** undergo the reaction to give allylated ketones **9** and **12** in ratios essentially unchanged from those of the substrates.[21a] These reactions were believed to proceed through oxidative addition of palladium to the allyl



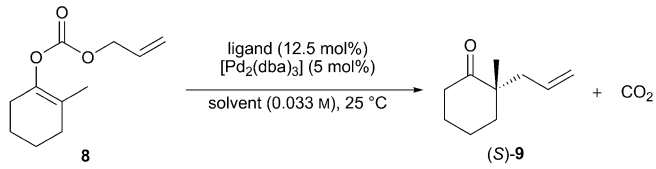
Scheme 3. Regiochemical fidelity in Tsuji's palladium-catalyzed allylation. i) [$Pd_2(dba)_3$], Ph_3P, dioxane.

fragment followed by loss of CO_2 to give {Pd^{II}-(allyl)} complex **13** and enolate **14**. However, the details involving the recombination of the ion pair to give cyclohexanone **9** and a palladium(0) species were unclear at the time of original reports by Tsuji and co-workers.[26] Coupled with the ability to purify the stable enolate precursors, we believed that the regiochemical fidelity afforded by the palladium-catalyzed reaction would provide direct access to enantioenriched α-quaternary ketones if a suitable chiral ligand could be found.[27]

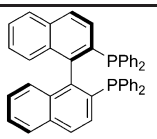
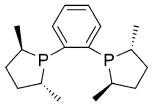
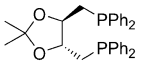
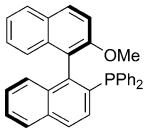
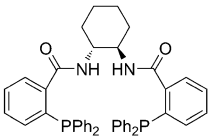
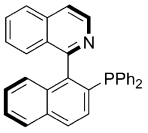
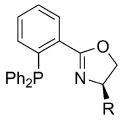
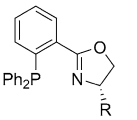
Results and Discussion

Initial screening of chiral ligands: Our initial goal was to show that a chiral ligand could transmit useful levels of asymmetric induction in the reaction while maintaining the important property of enolate regiochemical fidelity found in the non-enantioselective system. We chose allyl enol carbonate **8** as a test substrate to evaluate the effect of various ligands (Table 1). Although allyl enol carbonates are less common than the other enolate precursors explored by Tsuji and co-workers, they allowed us to add a single, achiral reagent to our catalyst system without extraneous initiators or counterions that might affect enantioselectivity, whereas silyl enol ether, enol acetate, and β-ketoester substrates did not. In accord with the reports by Tsuji and co-workers, we performed our initial trials in dioxane. Due to the prevalence of bis(phosphine) ligands in asymmetric catalysis, we began with several privileged bis(phosphine) ligands, but found that only the Trost ligand (**6**) gave a significant *ee*. However, commercially available (*R*)-QUINAP (**15**), a chelating N/P-type ligand,[28] gave less variation in *ee* across other ethereal solvents (compare Table 1, entries 5 and 6 in dioxane and THF). Encouraged by this result, we quickly found that the phosphinooxazoline (PHOX) class of N/P-type ligands also provided excellent reactivity and promising levels of enantioselectivity. The numerous readily available amino acid derived PHOX ligands[29] allowed us to rapidly discover that bulkier aliphatic groups on the oxazoline provided higher levels of enantioinduction, with (*S*)-*t*Bu-PHOX (**19**) providing α-quaternary ketone (*S*)-**9** in 86% *ee* with dioxane as the solvent. Additionally, we observed slightly higher *ee* values in reactions with (*R*)-*i*Pr-PHOX (**17**) and (*S*)-*t*Bu-PHOX (**19**) if THF was used as the solvent (83 and 88% *ee*, respectively).[30] Having attained satisfying levels of enantio- and regioselectivity in forming ketone **9**, we began a more thorough investigation of the reaction conditions.

Table 1. Initial ligand screening.[27a]



8 (*S*)-**9**

	Ligand		1,4-Dioxane *t* [h]	Yield [%][a]	*ee* [%][b]	Tetrahydrofuran *t* [h]	Yield [%][a]	*ee*[b] [%]
1		(*R*)-BINAP	5	92	5[c]	5	76	2[c]
2		(*R*,*R*)-Me-DUPHOS	5	61	0	5	66	0
3		(*R*,*R*)-DIOP	2	91	2[c]	2	59	2[c]
4		(*R*)-MOP	3	93	18	3	47	13
5		(*R*,*R*)-Trost ligand (**6**)	2	97	46[c]	5	92	64[c]
6		(*R*)-QUINAP (**15**)	2	98	61	2	97	61
7		(*R*)-Ph-PHOX (**16**; R=Ph)	2	95	62[c]	2	95	65[c]
8		(*S*)-*i*Pr-PHOX (**17**; R=*i*Pr)	3	96	82[c]	2	95	83[c]
9		(*R*)-Bn-PHOX (**18**; R=Bn)	3	96	65	5	94	63
10		(*S*)-*t*Bu-PHOX (**19**; R=*t*Bu)	2	95	86	2	96	88

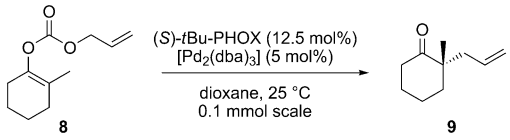
[a] GC yield of **9** relative to an internal standard (tridecane). [b] Enantiomeric excess by chiral GC. [c] (*R*)-**9** produced as the major product.

Optimization of reaction parameters: The straightforward experimental procedure for asymmetric alkylation provided several opportunities to optimize the reaction. One important experimental parameter was found to be the complexation time for (*S*)-*t*Bu-PHOX (**19**) and tris(dibenzylideneacetone)dipalladium(0) ([Pd_2(dba)$_3$]) prior to addition of the substrate.[31] Mixing the metal and ligand for 30 min before substrate addition resulted in a balance between short complexation times (e.g., 5 min) in which lower yields but complete consumption of the substrate were observed, and longer complexation times (e.g., 1–3 h) in which poor conversion was observed. Storing the ligand–metal complex for

an extended time seemed to be complicated by the introduction of adventitious amounts of O_2 that readily oxidized the ligated PHOX molecule at phosphorus, thereby preventing significant consumption of the starting material.[32]

We also investigated the effect of concentration on the reaction (Table 2). At higher concentrations, significantly lower yields were observed, as well as slightly decreased *ee*. No further increase in enantioselectivity was observed below 0.03 M.

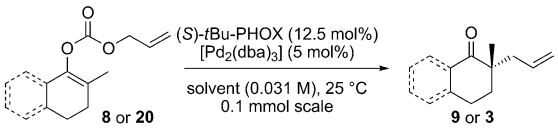
Table 2. Effect of concentration on asymmetric allylation.[a]



	Concentration [M]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	0.500	3	81	82
2	0.250	2	90	84
3	0.125	2	94	84
4[d]	0.063	2	99	85
5	0.031	2	95	86

[a] Unless otherwise noted, data reported are the average of three experiments. [b] GC yield relative to an internal standard (tridecane). [c] Enantiomeric excess measured by chiral GC. [d] Data reported are the average of two experiments.

Table 3. Effect of solvent on asymmetric allylation.



	Solvent	9[a,b]			3[a,b]	
		t [h]	Yield [%][c]	*ee* [%][d]	*t* [h]	*ee* [%][e]
1	1,4-dioxane	2	95	86	1	87
2	tetrahydrofuran	2	96	88	1	88
3	diethyl ether	2	98	89	1	80
4	*tert*-butyl methyl ether	2	98	89	1	78
5	diisopropyl ether	2	95	89	–	–
6	anisole	3	82	81	–	–
7	1,2-dimethoxyethane	2	72	56	–	–
8	benzene	2	99	88	1	89
9	toluene	2	99	88	1	87
10	ethyl acetate	2	97	86	–	–
11	acetone	3	26	60	–	–
12	triethylamine	2	72	89	–	–
13	fluorobenzene	3	58	51	–	–
14	dichloromethane	3	42	13	–	–
15	chloroform	6	0	–	–	–

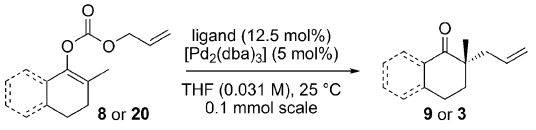
[a] Data reported are the average of three experiments. [b] All reactions proceeded to complete conversion except entries 13–15. [c] GC yield relative to an internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Enantiomeric excess measured by chiral HPLC.

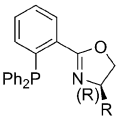
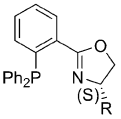
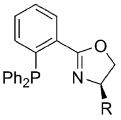
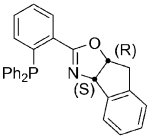
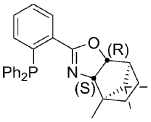
Encouraged by our initial discovery that reactions in THF gave better levels of enantioinduction than those in dioxane, we undertook a more thorough study of solvent effects on the reaction (Table 3). Many of the ethereal solvents investigated gave good results. Diethyl ether, *tert*-butyl methyl ether (TBME), and diisopropyl ether all provided good yields and slightly higher *ee* values than reactions in THF with allyl enol carbonate **8** (Table 3, entries 3–5). However, methyl tetralone derived allyl enol carbonate **20** yielded products with substantially lower *ee* values in diethyl ether and TBME. The poor solubility of the catalyst in these less coordinating ethereal solvents occasionally led to incomplete conversion, a disadvantage that outweighed the slight increase in *ee*. Interestingly, several non-ethereal solvents also performed well in the transformation. Reactions in benzene and toluene gave similar yield and enantioinduction to those in THF (Table 3, entries 8 and 9). The reaction also tolerated carbonyl-containing solvents; ethyl acetate (Table 3, entry 10) provided good yields and enantioselectivity in the asymmetric allylation, although acetone (Table 3, entry 11) afforded an inferior yield and *ee*. Interestingly, triethylamine produced a level of enantioselectivity equal to that observed with the best ethereal solvents, albeit in lower yield (Table 3, entry 12). Halogenated solvents fared poorly in the reaction, suffering from low conversion and yield (Table 3, entries 13–15). Overall, we were intrigued by the variety of solvents with vastly different properties that performed equally well.

Fine tuning of the phosphinooxazoline ligands: Substantial effort was invested in improving the enantioselectivity of the reaction by modifying the structure of the PHOX ligand (Table 4).[33] Hoping to continue the trend of increasing enantioselectivity initially noted in moving from *i*Pr- to *t*Bu-PHOX (Table 4, entries 2 and 4), we carried out the synthesis of numerous PHOX ligands with varied steric environments and evaluated these ligands in the reaction of allyl enol carbonates **8** and **20**. In general, ligands containing saturated substituents on the oxazoline fragment performed better than those with aryl groups in terms of *ee*. Moving the steric bulk away from the oxazoline framework by inserting a methylene group (i.e., ligand **23**, Table 4, entry 6) substantially lowered the enantioselectivity. Of particular note are L-serine-derived ligands **27** and **28** (Table 4, entries 10 and 11),[34] which allowed access to the enantiomeric (*R*) product series with nearly the same level of enantioselectivity as that observed with (*S*)-*t*Bu-PHOX (**19**), but without the need for the more costly (*R*)-*tert*-leucine (**21**).[35] The known *cis*-1-aminoindan-2-ol-derived ligand **29** and borneol-derived ligand **30**, both with uniquely shaped substituents, gave slightly lower enantioselectivity relative to *t*Bu-PHOX (**19**).[36] It is noteworthy that regardless of the shape or type of substituent on the PHOX ligand, the ketone products contained quaternary stereocenters with a consistent sense of configuration (e.g., (*S*)-PHOX ligands provide (*S*)-**9**).[37] With *t*Bu-PHOX (**19**) established as the optimal steric framework, we next considered the electronics of the ligand.[38]

A number of *t*Bu-PHOX derivatives were synthesized to probe the importance of phosphine electronics (Table 5). We investigated ligands ranging from electron-rich to electron-poor phosphines with allyl enol carbonates **20** and **8**

Table 4. Effect of phosphinooxazoline sterics on enantioselective alkylation (Cy = cyclohexyl; Bn = benzyl; TBS = *tert*-butyldimethylsilyl).



	Ligand		Product[a]	*ee* [%][b]
1		**16**; R = Ph	**9**	65 (*R*)
2		**17**; R = *i*Pr	**9**	83 (*R*)
3		**18**; R = Bn	**9**	63 (*S*)
4		**19**; R = *t*Bu	**9**	88 (*S*)
5[c]		**22**; R = 1-adamantyl	**3**	78 (*S*)
6		**23**; R = CH_2*t*Bu	**3**	59 (*S*)
7		**24**; R = CH_2(1-naphthyl)	**9**	41 (*S*)
8		**25**; R = Cy	**9**	83 (*R*)
9		**26**; R = $CHPh_2$	**9**	69 (*R*)
10		**27**; R = $C(Me)_2OBn$	**3**	85 (*R*)
11		**28**; R = $C(Me)_2OTBS$	**3**	85 (*R*)
12		**29**	**3**	79 (*S*)
13		**30**	**3**	81 (*S*)

[a] All reactions proceeded to complete conversion. [b] Enantiomeric excess measured by chiral HPLC or GC. [c] Reaction run at 0.2 M in dioxane.

(Table 5, entries 1–7 and 8–14, respectively). The electronic perturbation had no significant effect on reaction yield, but ligands bearing electron-withdrawing groups (especially CF_3 groups) gave a significant increase in the rate of the reaction with allyl enol carbonate substrates.[33a] Furthermore, electron releasing *para* substituents on the phenyl rings tended to lower the *ee* values of the product relative to that observed with (*S*)-*t*Bu-PHOX (Table 5, entries 1 and 8). If tetralone-derived allyl enol carbonate **20** was used as the substrate, a slight increase in enantioselectivity was observed with electron-withdrawing substituents at the *para*-phenyl positions (Table 5, entries 3–5). However, the enantioselectivity decreased significantly with extremely electron-poor PHOX ligands (Table 5, entries 6 and 7). This trend was not apparent in the enantioselectivity with cyclohexyl-derived allyl enol carbonate **8** (Table 5, entries 8–14). These results suggest a subtle interplay between ligand and substrate electronics.

As a final perturbation of the PHOX ligand structure, we prepared a number of non-N/P mixed chelates based on the phenyl oxazoline skeleton of the PHOX ligands (Table 6).[39] The phosphine oxide of *t*Bu-PHOX is inactive as a catalyst in this reaction.[32] A sulfur analogue also failed to catalyze the reaction (Table 6, entry 1).[40] Moving down the periodic table from phosphorus, the arsenic analogue of *t*Bu-PHOX had excellent activity as a catalyst, but gave tetralone **3** in only moderate *ee* (Table 6, entry 2). A nitrogen analogue showed little catalytic activity, and the small amount of product generated was nearly racemic (Table 6, entry 3). As a final derivative that maintains the six-membered ring chelation pattern, but changes the hybridization of the backbone atoms involved, a known phosphinite ligand, Simple-PHOX, was found to give only a moderate *ee* value (Table 6, entry 4).[41]

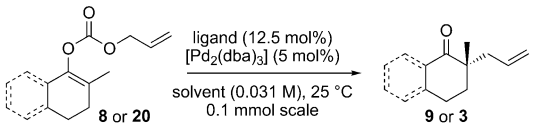
Although some electron-deficient derivatives of *t*Bu-PHOX did provide slightly better product *ee* values with certain substrates, ultimately this slight improvement did not typically offset the added difficulty in synthesizing the substituted PHOX ligands.[33] Our studies clearly showed that N/P chelates were particularly effective at inducing high levels of asymmetry in the allylation reaction. As a result, we retained the use of (*S*)-*t*Bu-PHOX (**19**) in our optimized conditions for exploring the scope of the reaction.

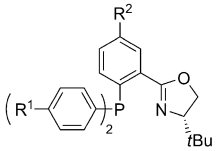
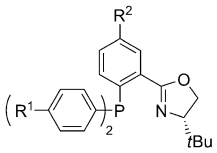
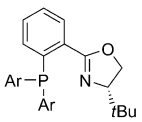
Asymmetric allylation of allyl enol carbonates: We have successfully employed a variety of allyl enol carbonates in our asymmetric Tsuji allylation (Table 7).[42] The allyl group may be substituted at the internal position, which results in slightly higher levels of asymmetric induction (Table 7, entry 4). The cyclic portion of the substrate may be unsaturated (Table 7, entry 5), substituted (Table 7, entries 6–11), appended to another ring (Table 7, entries 12 and 13), or enlarged (Table 7, entries 14 and 15). Among these variations, several are particularly noteworthy: the presence of a conjugated acceptor enone (Table 7, entry 5) does not lead to Michael addition products, highlighting the essentially neutral reaction conditions; quaternary stereocenters may be synthesized vicinal to pre-existing, fully substituted carbon atoms (Table 7, entry 8); the temperature may be lowered in order to improve enantioselectivity if highly reactive substrates are employed (Table 7, entries 12 and 13), although the reaction time increases significantly.[43] Overall, we were pleased to find that a wide range of functionalized, enantioenriched cycloalkanones were accessible by this method.

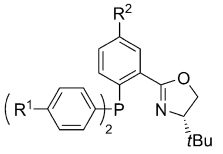
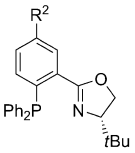
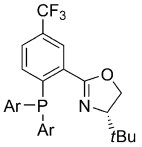
Our use of allyl enol carbonates enabled direct access to α-quaternary ketones with multiple acidic sites. However, allyl enol carbonates are rarely encountered in the literature, and the synthesis of isomerically pure enol carbonates[44] often required the synthesis of silyl enol ethers as intermediates. Because Tsuji and co-workers used silyl enol ethers in their non-enantioselective allylation, we contemplated adapting our reaction conditions so that silyl enol ethers could be employed directly.

Asymmetric allylation of silyl enol ethers: Silyl enol ethers are commonly encountered enolate equivalents. Unlike allyl enol carbonates, silyl enol ethers render the alkylation reaction intermolecular, with the enolate precursor and allyl fragment introduced separately. We discovered in our initial studies that silyl enol ethers were not sufficiently nucleophilic to react with the {Pd^{II}(allyl)} fragment under our reaction

Table 5. Effect of phosphine electronics on enantioselective alkylation.[a]

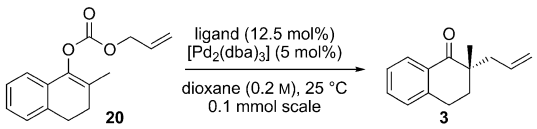


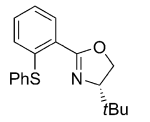
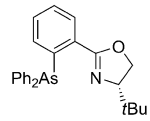
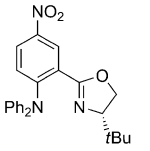
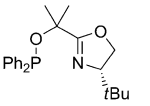
	Product	Ligand		Solvent	*ee* [%][b]
1	**3**		**31**; R^1 = Me; R^2 = H	1,4-dioxane	81
2	**3**		**19**; R^1 = H; R^2 = H	1,4-dioxane	87
3	**3**		**32**; R^1 = F; R^2 = H	1,4-dioxane	88
4	**3**		**33**; R^1 = CF_3; R^2 = H	1,4-dioxane	89
5	**3**		**34**; R^1 = H; R^2 = NO_2	1,4-dioxane	90
6	**3**		**38**; Ar = *m*-$(CF_3)_2C_6H_3$	1,4-dioxane	83
7	**3**		**39**; Ar = C_6F_5	1,4-dioxane	81

	Product	Ligand		Solvent	Yield [%][c]	*ee* [%][d]
8	**9**		**35**; R^1 = H; R^2 = OMe	THF	99	86
9	**9**		**19**	THF	96	88
10	**9**		**36**; R^1 = H; R^2 = CF_3	THF	99	89
11	**9**		**32**	THF	95	88
12[e]	**9**		**33**	THF	97	87
13[e]	**9**		**34**	THF	89	88
14	**9**		**37**; Ar = *p*-$(CF_3)C_6H_4$	THF	99	87

[a] All reactions proceeded to complete conversion. [b] Enantiomeric excess measured by chiral HPLC. [c] GC yield relative to an internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Data reported are the average of two experiments.

Table 6. Effect of varied heteroatom chelates on enantioselective alkylation.



	Ligand	Conversion [%]	*ee* [%][a]
1		0[b]	–
2		99[b]	52
3		<5[b]	7
4		87[c]	56

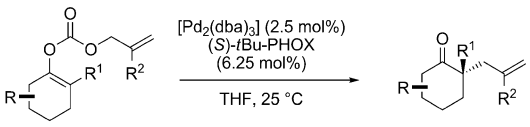
[a] Enantiomeric excess measured by chiral HPLC. [b] Conversion estimated by TLC analysis. [c] Experiment performed with allyl enol carbonate **8**. Conversion measured by GC relative to an internal standard (tridecane). Enantiomeric excess measured by chiral GC.

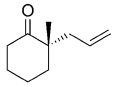
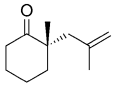
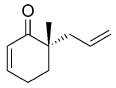
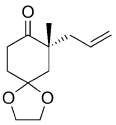
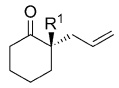
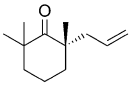
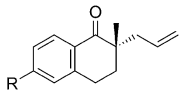
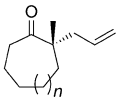
conditions at 25 °C. However, we found that the reaction could be initiated in the presence of tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT), a commercially available dry fluoride source.

The use of TBAT as an initiator complicated the proposed catalytic cycle (Scheme 4). In the case of allyl enol carbonates, the oxidative addition of allyl carbonate **8** and rapid decarboxylation led directly to the enolate/{Pd^{II}(allyl)} ion pair, which could collapse directly into the product (Scheme 3). For the intermolecular reaction, we primarily used diallyl carbonates as the allyl precursors, although mixed carbonates were also effective. Oxidative addition of allyl carbonates occurs readily at 25 °C to give {Pd^{II}(allyl)} species **13**, CO_2, and an alkoxide. The addition of TBAT immediately generates the enolate, which can react with palladium complex **13** by the same enantioselective mechanism observed for allyl enol carbonates. A substoichiometric amount of TBAT was sufficient, because the alkoxide formed in the reaction is also capable of providing the enolate in situ. In principle, it should be possible for the small amount of allyl alkoxide generated from oxidative addition to initiate the reaction.[45] In practice, we found that 35 mol% TBAT was usually sufficient to ensure complete conversion of the silyl enol ether (**40**). Having developed an effective means of silyl enol ether activation, we attempted the asymmetric alkylation with a range of tetrasubstituted silyl enol ethers.

Gratifyingly, alkylation of the silyl enol ether substrates occurred with levels of enantioinduction similar to those observed for the allyl enol carbonate substrates and over a similar range of substrates (Table 8). Specifically, methyl- and ethyl-substituted quaternary ketones were produced with the same *ee* observed in the allyl enol carbonate reactions (Table 8, entries 1 and 2). A tertiary ether stereocenter was accessible from an α-oxygenated silyl enol ether, albeit with moderate *ee* (Table 8, entry 3). In addition to diallyl

Table 7. Substrate scope for the asymmetric allylation of allyl enol carbonates.[27a]

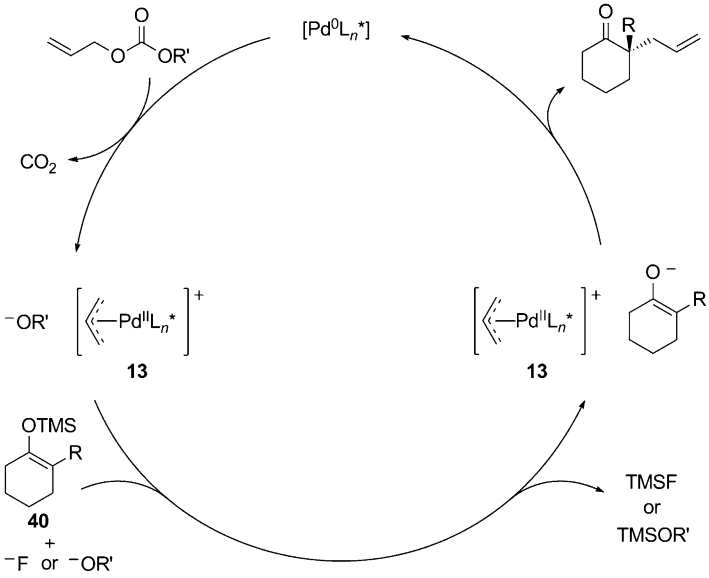


	Product[a]		Yield [%][b]	*ee* [%][c]
1			85	87
2[d]			85	86 (96)[e]
3[f]			90	89
4[g]			89	91
5			91	89
6			87	86
7		$R^1 = CH_2CH_3$	96	92
8[g]		$R^1 = t$Bu	55[h]	82
9		$R^1 = CH_2Ph$	96	85
10		$R^1 = (CH_2)_3OBn$	87	88
11			94	92
12[i]		R = H	87	91
13[i]		R = OCH_3	94	91
14		$n = 1$	81	87
15		$n = 2$	90	79

[a] Reactions were performed by using the substrate (1.0 mmol) in THF (0.033 M in substrate) at 25 °C with $[Pd_2(dba)_3]$ (2.5 mol %) and (*S*)-*t*Bu-PHOX (**19**; 6.25 mol %), unless otherwise noted. Each reaction was complete in 1–10 h. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Performed on a 5.1 mmol scale. [e] % *ee* after one recrystallization of the corresponding semicarbazone is given in parentheses. [f] Reaction performed at 12 °C (GC yield). [g] Performed with 5 mol % $[Pd_2(dba)_3]$ and 12.5 mol % (*S*)-**19**. [h] Isolated yield after conversion to the corresponding diketone through Wacker oxidation. [i] Performed at 10 °C.

carbonate, dimethallyl carbonate served as a suitable allyl fragment precursor (Table 8, entries 4 and 5). Interestingly, 2-allyl-2-methallylcyclohexanone, containing only a remote methyl group to engender chirality, formed in 91 % *ee*. As with the reactions of allyl enol carbonates, substitution on the ring and larger ring sizes were tolerated as well (Table 8, entries 6–8).

In addition to the flexibility afforded by the intermolecular reaction of silyl enol ethers with diallyl carbonates, the use of silyl enol ethers as a means to generate enolates independent of the allyl fragment allowed the catalytic cycle to commence at the stage of $\{Pd^{II}(allyl)\}$ complex **41** (Scheme 5). Upon mixing (*S*)-*t*Bu-PHOX, $[\{Pd(allyl)Cl\}_2]$,

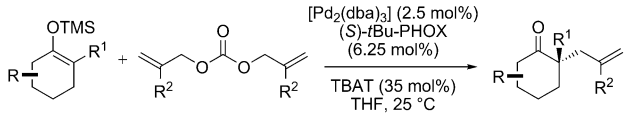


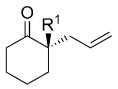
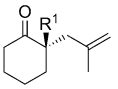
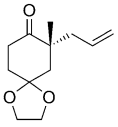
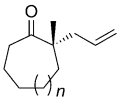
Scheme 4. General catalytic cycle for silyl enol ether alkylation.

and NH_4PF_6 in ethanol,[46] $[Pd^{II}(allyl)PHOX]^+[PF_6]^-$ salt **41** readily precipitated, and this solid could be recrystallized and characterized crystallographically as a partial EtOH adduct.[47] Complex **41** serves as a precatalyst in the enol silane variant of our enantioselective alkylation reaction, giving a good yield and a nearly identical product *ee* compared to that observed with the in situ generated catalyst. The $\{Pd^{II}\}[PF_6]$ salt **41** has several practical advantages. It is an air stable, non-hygroscopic solid that may be stored indefinitely. Moreover, the use of the preformed [Pd(allyl)PHOX] catalyst obviated the introduction of dibenzylideneacetone (dba), which often complicated the purification of the α-quaternary ketone products.[48]

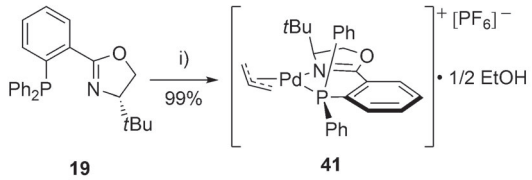
Enantioselective alkylation of dioxanone substrates for the synthesis of tertiary ethers and alcohols: Given our success in preparing α-quaternary cycloalkanones, we wished to explore the direct synthesis of enantioenriched α-oxygenated ketones, which are a particularly challenging structure and appear in a number of biologically active compounds.[49] Our preliminary attempts to form these systems included a Baeyer–Villiger oxidation of an α-quaternary ketone (see below) and a single example of an oxygenated enol silane that provided a tertiary ether in only moderate *ee* (Table 8, entry 3). The latter result indicated that an exocyclic heteroatom directly attached to the putative enolate intermediate caused significant disruption of the stereocontrolling elements of the catalyst. Therefore, we chose to explore a class of substrates with the heteroatom contained within the ring, a position from which it would be less likely to interact with the metal center.[27c] Dioxanone substrates have been employed in chiral-auxiliary-controlled enolate alkylations, and we hypothesized that our catalytic enolate-alkylation procedure might provide a more efficient route to these oxygenated products.[50,51]

Table 8. Substrate scope for asymmetric allylation of silyl enol ethers.[27a]

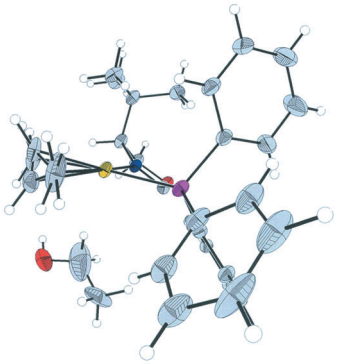


	Product[a]		Yield [%][b]	*ee* [%][c]
1		$R^1 = CH_3$	95	87
2		$R^1 = CH_2CH_3$	96	92
3		$R^1 = OBn$	83	59
4[d]		$R^1 = CH_3$	79	91
5[d]		$R^1 =$ allyl	82	91
6			99	81
7		$n = 1$	94	86
8		$n = 2$	96	79

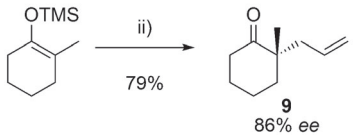
[a] Reactions were performed by using the substrate (1.0 mmol) in THF (0.033 M in substrate) at 25 °C with $[Pd_2(dba)_3]$ (2.5 mol %), (*S*)-*t*Bu-PHOX (**19**; 6.25 mol %), diallyl carbonate (1.05 equiv), and TBAT (35 mol %), unless otherwise noted. Each reaction was complete in 2–5 h. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Reaction performed with dimethallyl carbonate (1.05 equiv).



19 **41**



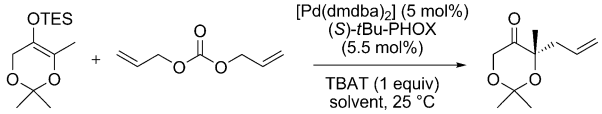
X-ray structure of **41**•(1/2 EtOH)



Scheme 5. Allylation with $\{Pd^{II}\}[PF_6]$ salt **41**. i) $[\{Pd(allyl)Cl\}_2]$, NH_4PF_6, EtOH, 22 °C; ii) **41** (10 mol %), diallyl carbonate, TBAT (37 mol %), THF, 25 °C, 1 h.

Consequently, we prepared enol silane **42** (Table 9) as a representative substrate of the dioxanone class.[52] We found that solvent had a larger effect on the yield and *ee* of the

Table 9. Effect of solvent on dioxanone alkylation (TES = triethylsilyl).



42 **43**

	Solvent	Yield [%][a]	*ee* [%][b]
1	tetrahydrofuran	40	81
2[c]	diethyl ether	59	89
3	1,4-dioxane	65	67
4	benzene	67	84
5	toluene	74	88

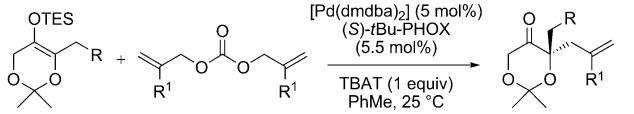
[a] Isolated yield from the reaction of the substrate (0.1 mmol) in a solvent (0.033 M in substrate) at 25 °C with $[Pd(dmdba)_2]$ (5 mol %), (*S*)-*t*Bu-PHOX (**19**; 5.5 mol %), diallyl carbonate (1.05 equiv), and TBAT (1 equiv), unless otherwise noted. Each reaction was complete in 5–7 h. [b] Measured by chiral HPLC of a derivative.[53] [c] Reaction performed at 30 °C.

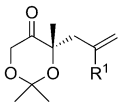
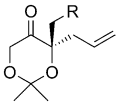
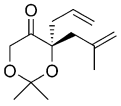
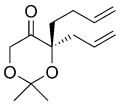
product with this class of substrate (Table 9) and that a full equivalent of TBAT was required for efficient conversion of the triethylsilyl (TES) enol ethers to the products. In the optimal case, exposure of enol ether **42** to the complex derived from $[Pd(dmdba)_2]$[48] (dmdba = 3,5,3′,5′-dimethyoxydibenzylideneacetone) and (*S*)-**19** in the presence of diallyl carbonate and TBAT (1 equiv) in toluene at 25 °C led to dioxanone product **43** in 74 % yield and 88 % *ee*. We explored the scope of this transformation and found that substitutions at the 2-position and on the allyl group were possible while maintaining high yields and *ee* values (Table 10). These oxygenated products were amenable to a number of subsequent transformations that enabled the enantioselective synthesis of several challenging structural motifs (see below).

Our work with silyl enol ethers demonstrated that our enantioselective process is robust enough to permit the introduction of the enolate and allyl fragments separately and to tolerate the presence of other ions in solution. Silyl enol ethers are a more familiar substrate class and greatly increase the practicality of the reaction. However, we rely on thermodynamically driven silyl enol ether syntheses, which typically produce a 10:1 ratio of isomers that requires somewhat tedious purification to obtain isomerically pure substrates.[44] A direct method for the synthesis of isomerically pure substrates would further increase the practicality of this catalyst system.[26] Nonetheless, the enantioselective alkylation reactions employing either allyl enol carbonate or enol silane substrates provide access to a broad range of enantioenriched α-quaternary cycloalkanones.

Asymmetric decarboxylative allylation of β-ketoesters: Encouraged by our previous results, we sought to exploit this technology for the preparation of a variety of interesting synthetic targets. In one such effort, we encountered difficulty in the preparation of the requisite enol carbonate or silyl

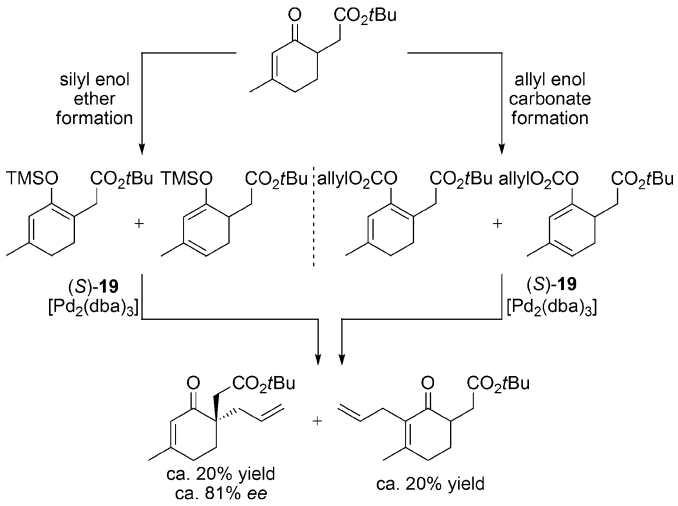
Table 10. Enantioselective alkylation by using dioxanone-derived enol silanes.[27c]



	Product[a]		Yield [%][b]	*ee* [%][c]
1		$R^1 = H$	86	87
2[d,e]		$R^1 = CH_3$	59	89
3[f]		$R^1 = Cl$	59	92
4[g]		$R^1 = Ph$	73	94
5		$R = CH_3$	79	93
6		$R = Ph$	85	86
7			88	85
8[e]			93	88
9			83	92

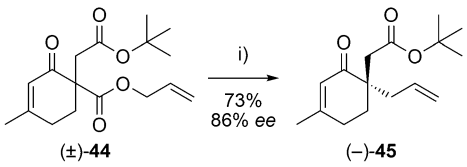
[a] Reactions were performed by using the substrate (0.5 mmol) in PhMe (0.033 M in substrate) at 25 °C with $[Pd(dmdba)_2]$ (5 mol %), (*S*)-*t*Bu-PHOX (**19**; 5.5 mol %), diallyl carbonate (1.05 equiv), and TBAT (1 equiv), unless otherwise noted. Each reaction was complete in 5–10 h. [b] Isolated yields. [c] Measured by chiral GC or HPLC, in some cases as a derivative.[53] [d] Reaction performed with the trimethyl silyl enol ether with TBAT (35 mol %) in Et_2O (0.0167 M in substrate). [e] Reaction performed with dimethallyl carbonate (1.05 equiv). The major product is the enantiomer of the structure shown. [f] Reaction performed with dichloroallyl carbonate (1.05 equiv) at 35 °C. [g] Reaction performed with diphenylallyl carbonate (1.05 equiv).

enol ether starting materials (Scheme 6). A variety of conditions for enolate formation and trapping led to inseparable mixtures of enol isomers. As a consequence of the high degree of regiochemical fidelity in the allylation reaction,[21,22] corresponding mixtures of allylated products were obtained. To address this problem, we sought a different class of substrates for our catalytic reaction that would rely on an alternative method of enolate generation that was: 1) specific for the production of the desired tetrasubstituted enolate, 2) did not rely on a thermodynamic equilibration under basic conditions, and 3) maintained high enantioselectivity in the overall transformation.



Scheme 6. Non-selective enolization leading to product mixtures.

Enantioselective alkylation with racemic allyl β-ketoesters: β-Ketoesters represent a classical solution to the problem of regioselective ketone alkylation (e.g., the acetoacetic ester synthesis).[54] In 1980, the groups of Tsuji and Saegusa reported allyl β-ketoesters as substrates in non-enantioselective Pd-catalyzed enolate alkylations.[21] We reasoned that an allyl β-ketoester might solve the problem of selective enolate formation in the course of an enantioselective allylation reaction. However, as stereogenic racemic substrates for a catalytic asymmetric reaction, allyl β-ketoesters presented some unique challenges: the catalyst must deallylate the substrate nonselectively to avoid kinetic resolution of the substrate, the C–C bond must break at a reasonable temperature in the decarboxylation step to prevent loss of selectivity in the subsequent bond-forming step, and the stereogenic intermediates must not experience diastereomeric transition states that are detrimental to the selectivity of the process.[55] Nonetheless, we prepared the appropriate substrate (**44**, Scheme 7) using standard methods[53] and exposed



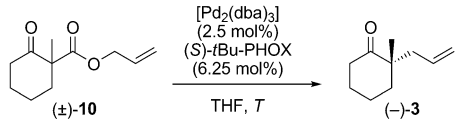
Scheme 7. Enantioselective decarboxylative alkylation with an allyl β-ketoester.[27b] i) (*S*)-**19** (6.25 mol %), $[Pd_2(dba)_3]$ (2.5 mol %), Et_2O, 30 °C, 9 h.

racemic (±)-**44** to our standard reaction conditions ($[Pd_2(dba)_3]$, (*S*)-*t*Bu-PHOX, THF, 25 °C). Unfortunately, no conversion was observed (by TLC) under these conditions after 24 h. However, we were delighted to find that elevating the temperature to 30 °C and carrying out the reaction in Et_2O restored reactivity, providing enone (–)-**45** in 73 % yield (>99 % conversion) and 86 % *ee* after 9 h. This experiment provided a key proof-of-concept for an enantioconvergent reaction by using a racemic allyl β-ketoester reagent.

While further exploring this pivotal reaction, we noted that no significant kinetic resolution of the allyl β-ketoesters was observed.[56] In fact, this facet of the reaction was critical to obtain a high yield in a reasonable reaction time. The similar levels of enantioselectivity observed with the allyl β-ketoester substrates and the other substrate classes (compare Tables 7 and 8 with Tables 12 and 13) suggest that the enantiodetermining transition state of the reaction remains unchanged. Although the extent to which decarboxylation

slowed at ambient temperature varied from substrate to substrate, β-ketoesters were uniformly more sluggish in decarboxylation than allyl enol carbonates.[57] However, the rate of reaction increased greatly at slightly higher temperatures, and thus reasonable reaction times (≈2 h) could be achieved by increasing the reaction temperature by about 5 °C, which had a negligible effect on the *ee* (Table 11).

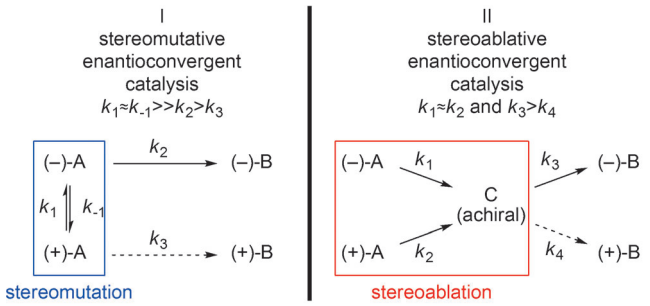
Table 11. The effect of the temperature on the decarboxylative allylation of allyl β-ketoesters.



	T [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	18	48	0	–
2	25	7.5	85	88
3	30	2.25	82	87
4	35	1.25	85	86
5	40	0.67	86	85
6	60	0.15	82	83

[a] Isolated yield from the reaction of the substrate (1.0 mmol) at 0.033 M. [b] Determined by chiral GC.

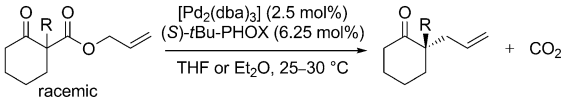
This enantioconvergent reaction is unusual due to the use of quaternary β-ketoesters (Scheme 8). Typical stereomutative enantioconvergent processes (e.g., dynamic kinetic resolution) involve a pre-equilibrium epimerization of the starting material, **A**, followed by enantioselective conversion to form product **B** (Pathway I).[58] However, quaternary stereocenters are not typically epimerizable, and we believe that both enantiomers of the starting material, **A**, convert irreversibly into a prochiral intermediate, **C**,[59] which preferentially forms one enantiomer of the product, **B**, under the influence of the chiral catalyst (Pathway II). We have termed such transformations stereoablative enantioconvergent processes due to a lack of an existing term to adequately describe this interesting reaction pathway.[60,61]



Scheme 8. Stereoablative enantioconvergent catalysis.

As a result of the facile synthesis of racemic quaternary β-ketoester substrates, we have been able to expand the substrate scope of the asymmetric alkylation greatly.[53] A number of α-substituted 2-carboxyallylcyclohexanones were readily prepared by the aforementioned methods and successfully underwent enantioconvergent decarboxylative allylation (Table 12). The system accomodated an array of functionality and substitution, and allowed the formation of products in excellent yield and high *ee*. Remarkably, the presumed enolate intermediate tolerated both enolizable (Table 12, entries 4 and 5) and β-heteroatom (Table 12, entry 9) substituents without the formation of side products corresponding to enolate scrambling or β-elimination.[62] Our conditions also allowed for incorporation of a fluorine atom for the high-yielding synthesis of a stereodefined tertiary fluoride (Table 12, entry 10). Following our initial disclosure, others have utilized this chemistry to prepare a range of tertiary fluoride-containing compounds that could be of interest as non-epimerizable pharmaceutical analogues.[42c,e,h,j,63]

Table 12. Enantioconvergent decarboxylative allylation of α-substituted 2-carboxyallylcyclohexanones.[27b]

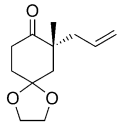
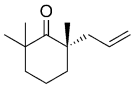
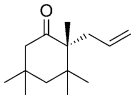
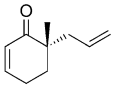
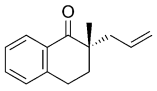
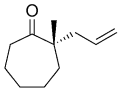
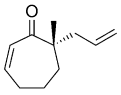
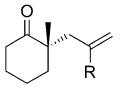
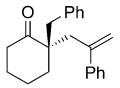
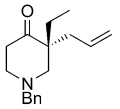
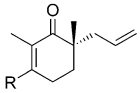
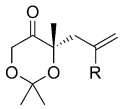


	R	*t* [h]	Yield [%][a]	*ee* [%][b]
1	CH_3	7.5	85	88
2[c]	CH_3	4.75	89	88
3[c,d]	prenyl	6	97	91
4[c]	CH_2CH_2CN	6.5	97	88
5[c,e]	$CH_2CH_2CO_2Et$	6	96	90
6	$CH_2C_6H_5$	0.5	99	85
7	$CH_2(4\text{-}CH_3OC_6H_4)$	10	80	86
8	$CH_2(4\text{-}CF_3C_6H_4)$	0.5	99	82
9[e]	$CH_2OTBDPS$	5	86	81
10[c,d]	F	3.5	80	91

[a] Isolated yield from reaction of the substrate (1.0 mmol) with [Pd_2(dba)$_3$] (2.5 mol %) and (*S*)-*t*Bu-PHOX (**19**; 6.25 mol %) at 0.033 M in THF at 25 °C, unless otherwise noted. [b] Enantiomeric excess determined by chiral GC or HPLC. [c] Performed in Et_2O. [d] Performed at 30 °C. [e] [Pd_2(dba)$_3$] (4 mol %), (*S*)-**19** (10 mol %) at 0.021 M.

In addition to modifications at the α-position of the substrate, the decarboxylative asymmetric allylation of β-ketoesters was also amenable to a wide variety of modifications to the carbocycle and allyl fragment (Table 13). In particular, the reaction was exceptionally tolerant of the steric demands of substitution at the 3-, 4-, 5-, and 6-positions of the cyclohexane ring; each position can be fully substituted without significantly affecting yield or enantioselectivity (Table 13, entries 1–4). Importantly for multi-step synthetic efforts, we found the protocol to be scalable with no detrimental effect on the results (Table 13, entry 2).[64] Unsaturated substrates (Table 13, entries 5 and 6), as well as substrates that contain seven-membered rings (Table 13, entries 7 and 8), performed well in the reaction. As with the previous substrate classes (i.e., allyl enol carbonates and silyl enol ethers), substitution at the central position of the allyl fragment had a beneficial effect on the enantioselectivity of the reaction (Table 13, entries 9–11).[65] The incorpora-

Table 13. Enantioconvergent decarboxylative allylation of β-ketoesters with substituted carbocycles and allyl fragments.[24e,f,27a]

	Product		Yield [%][a]	*ee* [%][b]
1			94	85
2[c]			94	86
3			89	90
4			90	85
5[d,e]			77	90
6[d]			97	92
7			83	87
8[f]			98	90
9[d,e]		R = CH_3	87	92
10[d,e]		R = Cl	87	91
11[g]			96	94
12			91	92
13[h]		R = *i*BuO	86	75
14[i]		R = PhS	85	92
15[d,j]		R = H	68	83
16[d,j]		R = Cl	97	91

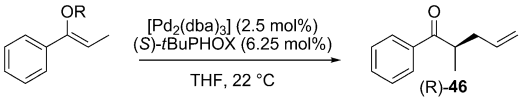
[a] Isolated yield from reaction of the substrate (1.0 mmol), [Pd_2(dba)$_3$] (2.5 mol%) and (*S*)-*t*Bu-PHOX (**19**; 6.25 mol%) at 0.033 M in THF at 25–35 °C, unless otherwise noted. Each reaction was complete in 1.5–12 h. [b] Determined by chiral GC or HPLC. [c] Substrate (25 mmol), [Pd_2(dba)$_3$] (1.5 mol%), and (*S*)-**19** (3.75 mol%), 24 h reaction time. [d] Performed in Et_2O. [e] [Pd_2(dba)$_3$] (4 mol%) and (*S*)-**19** (10 mol%) at 0.021 M. [f] Substrate (3.17 mmol), [Pd(dmdba)$_2$] (3 mol%), and (*S*)-**19** (3.8 mol%) at 0.060 M. [g] [Pd(dmdba)$_2$] (2.5 mol%) and (*S*)-**19** (2.5 mol%). [h] [Pd_2(pmdba)$_3$] (2.5 mol%) and (*S*)-**19** (6.25 mol%) in PhMe at 80 °C. [i] [Pd_2(pmdba)$_3$] (2.5 mol%) and (*R*)-**19** (6.25 mol%) in PhMe at 50 °C; major product was the enantiomer of the shown structure. [j] [Pd(dmdba)$_2$] (5 mol%) and (*S*)-**19** (6.25 mol%).

tion of a chlorine atom on the allyl fragment (Table 13, entry 10) provides both another functional group handle for further manipulation and a higher oxidation state. Inclusion of a phenyl group on the allyl fragment (Table 13, entry 11) produced the highest *ee* product we have observed to date (94% *ee*). Heterocyclic compounds were also accessible by this method (Table 13, entry 12). Vinylogous esters were competent in the reaction, but elevated temperatures (up to 80 °C) were required in some cases to achieve high conversion and the *ee* was somewhat decreased (Table 13, entry 13). However, employing a vinylogous thioester lowered the required temperature and permitted the isolation of a highly enantioenriched product (Table 13, entry 14).[66] This particular vinylogous thioester was employed in the enantioselective syntheses of (+)-carissone[24e] and (+)-cassiol[24f] (see below). We have demonstrated that dioxanones are viable substrates as well (Table 13, entries 15 and 16). The tetrasubstituted α-alkoxycarbonyl products were furnished in good yields and enantiomeric excesses, and the products could be readily derivatized to give a number of enantioenriched α-hydroxycarbonyl compounds.[27c]

Challenging Substrate Classes

Synthesis of tertiary stereocenters from acyclic enolate precursors: Although we have principally employed our asymmetric allylation for the synthesis of fully substituted stereocenters, the mild and nearly neutral conditions of the reaction are well suited for the synthesis of tertiary stereocenters α to carbonyls (Table 14).[67] This type of stereocenter is prone to epimerization and over-alkylation under the strongly basic conditions traditionally used for enolate generation.[68] We found that the allyl enol carbonate underwent allylation to form phenyl ketone (*R*)-**46** in 67% *ee* (Table 14, entry 1). In analogy to the results of Hou and co-workers,[18e] we found that the addition of AgBr gave a significant increase in the *ee* of the product (Table 14, entry 2). Both trimethylsilyl (TMS)[69] and *tert*-butyldimethylsilyl (TBS)[70] enol

Table 14. Enantioselective allylation of allyl enol carbonates and silyl enol ethers not contained in a ring.



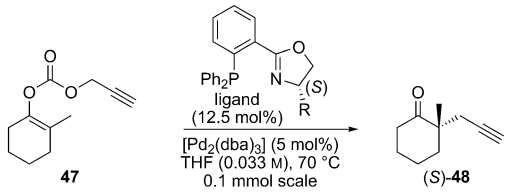
	R	Additive	Yield [%][a]	*ee* [%][b]
1	CO_2allyl	none	79	67
2	CO_2allyl	AgBr[c]	75	79
3[d]	TMS	TBAT[e]	60	62
4[d]	TBS	TBAT[e]	82	73
5[d]	TMS	CsF[f]	79	77
6[d]	TMS	CsF[f]; AgBr[c]	20	79
7[d,g]	TMS	CsF[f]	38	82

[a] Isolated yield from reactions with the substrate (0.092 mmol) in THF (0.092 M) with [Pd_2(dba)$_3$] (2.5 mol%) and (*S*)-*t*Bu-PHOX (**19**; 6.25 mol%), unless otherwise noted. [b] Measured by chiral HPLC. [c] 40 mol% additive. [d] Reaction performed with diallyl carbonate (1.05 equiv). [e] 35 mol% additive. [f] 48 mol% additive. [g] Performed in Et_2O.

ethers were successful as enolate precursors if TBAT was used as an initiator (Table 14, entries 3 and 4). Unlike the tetrasubstituted silyl enol ethers, CsF proved to be the optimal fluoride source for the less substituted silyl enol ethers, resulting in noticeably higher *ee* values (Table 14, entry 5). Unfortunately, the use of AgBr in the presence of CsF greatly reduced reactivity and only slightly increased the product *ee* (Table 14, entry 6). Similarly, the use of diethyl ether as a solvent increased the enantioselectivity at the expense of yield (Table 14, entry 7). Although our allylation methods have provided tertiary stereocenters in only moderate *ee*, we have recently disclosed a complementary decarboxylative protonation of quaternary allyl β-ketoesters based on a similar catalyst system that provides access to tertiary stereocenters α to ketones in excellent *ee*.[71]

Application of the palladium–PHOX catalyst system to propargylation: In addition to allylation, we also explored propargylation of enol carbonates with the Pd–PHOX catalyst system (Table 15).[72] Our preliminary studies show that

Table 15. Enantioselective propargylation.



47 (S)-48

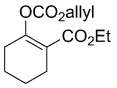
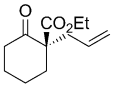
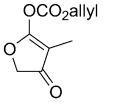
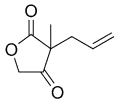
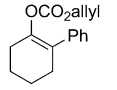
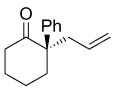
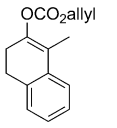
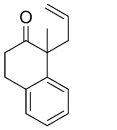
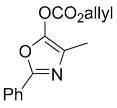
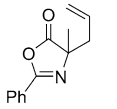
	Ligand	Yield [%][a]	*ee* [%][b]
1	**19**, R = *t*Bu	84	12
2	**23**, R = CH_2*t*Bu	83	32
3	**18**, R = CH_2Ph	54	26
4	**24**, R = CH_2(1-naphthyl)	57	37
5	**49**, R = CH_2(2-naphthyl)	71	26
6	**50**, R = CH_2(3,5-(*t*Bu)$_2$Ph)	94	25
7	**51**, R = CH_2(9-anthracenyl)	80	44

[a] GC yield relative to an internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC. In all cases, (*S*)-**48** was the major enantiomer.

propargylation of enol carbonate **47** required significantly higher temperatures than are required for allylation.[73] Additionally, the optimal structure of the PHOX ligand is significantly different for propargylation than for allylation. Moving the bulk of the *t*Bu group away from the oxazoline by insertion of a methylene group gave (*S*)-**48** in higher *ee* (Table 15, entries 1 and 2). Unlike allylation (compare with Table 4), PHOX ligands prepared from phenylalanine derivatives gave higher *ee* products than those prepared from saturated amino acids, with 9-anthracenylalanine derivative **51** giving the highest level of enantioselectivity (Table 15, entry 7). Although still preliminary, these studies suggest that the Pd–PHOX catalyst system may find uses with electrophiles other than allyl groups.[27e,71]

Substrates proceeding via weakly basic enolates: The alkylation of substrates derived from ketones of unusually low pK_a (i.e., stabilized enolates) as a group gave by far the lowest levels of enantioselectivity we have observed with the Pd–PHOX catalyst system (Table 16). Despite the low

Table 16. Asymmetric alkylation via stabilized allyl enol carbonates.

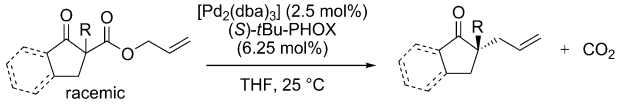
	Substrate	Product	Yield [%][a]	*ee* [%][b]
1			89	24[c]
2			87	2
3			99	11[c]
4			93	0
5			89	2

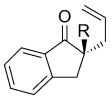
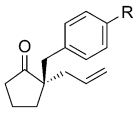
[a] Isolated yield from reaction of the substrate (1.0 mmol) in THF (0.033 M) at 25 °C with [Pd_2(dba)$_3$] (2.5 mol %) and (*S*)-*t*Bu-PHOX (**19**; 6.25 mol %). Each reaction was complete in 2 h. [b] Measured by chiral GC or HPLC. [c] Absolute stereochemistry of products assigned by analogy.

enantioselectivity, these substrates consistently gave excellent yields of the allylated products. It is noteworthy that the β-ketoester (Table 16, entries 1 and 2) and α-aryl ketone (Table 16, entries 3 and 4) derived enolates, which gave excellent enantioselectivity in the asymmetric allylation reactions previously published by Trost and co-workers,[15,16b] failed to give useful levels of enantioinduction under our conditions.[74] An oxazole substrate, designed with the intention of performing an enantioselective synthesis of α,α-disubstituted amino acids, also underwent allylation with little enantioselectivity, presumably due to the stability of the intermediate aromatic enolate (Table 16, entry 5). The orthogonality of the substrate scope, in terms of asymmetric induction, between our method and the early reports by Trost and co-workers may be indicative of fundamentally different mechanisms underlying the two allylation reactions and is an important piece of evidence in our mechanistic hypothesis.[26,75]

Substrates containing five-membered rings: Although enolate precursors contained in six-membered rings composed the bulk of our substrates, we have demonstrated that seven- and eight-membered rings are tolerated with only a slight decrease in *ee* (see Tables 7, 8, and 13). Allyl β-ketoesters constructed on five-membered rings provided modest to useful levels of enantioselectivity (Table 17). These sub-

Table 17. Enantioconvergent decarboxylative allylation of β-ketoesters containing five-membered rings.



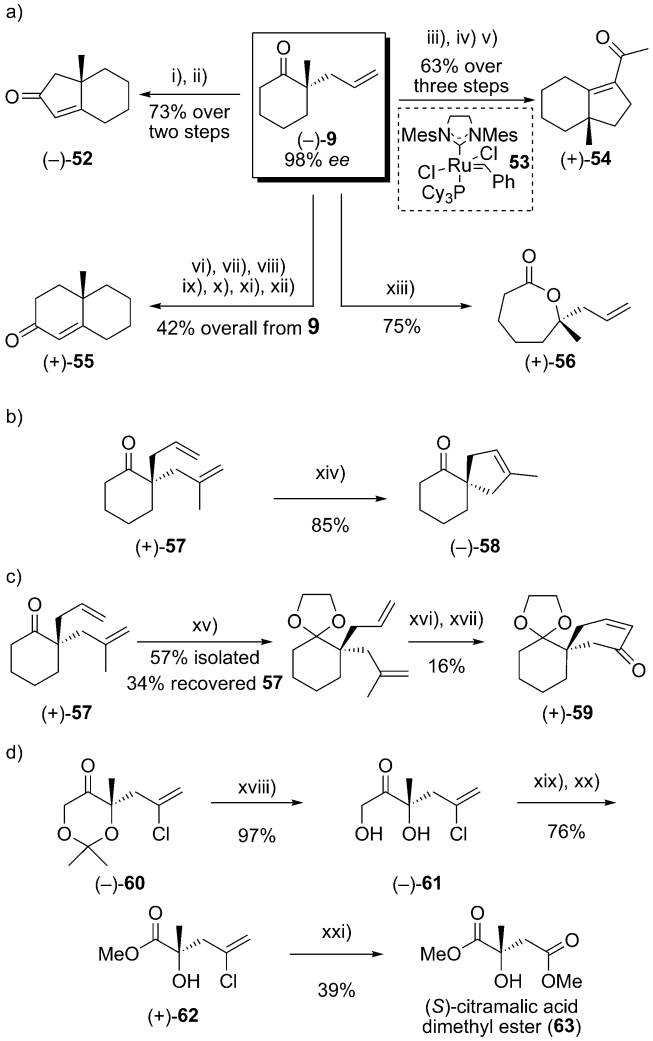
	Product		Yield [%][a]	*ee* [%][b]
1		R = CH_2CH_3	82	86
2		R = $CH(CH_3)_2$	77	84
3		R = CH_2NPhth	67	48
4[c]		R = Me	82	80
5		R = Bn	93	71
6		R = OMe	84	73
7		R = Me	84	73
8		R = CF_3	83	60

[a] Isolated yield from reaction of the substrate (1.0 mmol) in THF (0.033 M) with $[Pd_2(dba)_3]$ (2.5 mol%) and (*S*)-*t*Bu-PHOX (**19**; 6.25 mol%), unless otherwise noted. Each reaction was complete in 1–3 h. [b] Enantiomeric excess measured by chiral GC or HPLC. [c] Performed on a 0.1 mmol scale with $[Pd_2(dba)_3]$ (5 mol%) and (*S*)-**19** (12.5 mol%).

strates generally produced α-quaternary ketone products in good yields with enantiomeric excesses about 10% lower than observed for the cyclohexanone analogue. Ethyl-substituted cyclopentanone was formed in 86% *ee*, only 6% lower than observed with the corresponding cyclohexanone (Table 17, entry 1). Indanones were produced in good yield and with useful *ee* values (Table 17, entries 4 and 5). Benzyl-substituted cyclopentanone substrates gave consistent yields, but electron-deficient aromatic rings decreased product *ee* more significantly than in the reactions of six-membered ring β-ketoesters (Table 17, entries 6–8).

Synthetic applications: The α-quaternary cycloalkanones produced in the asymmetric Tsuji alkylation are very useful chiral building blocks. Each product contains at least two functional groups, a ketone and an olefin, for further manipulation. Moreover, the preceding section of this paper has shown these allylation reactions to be highly functional-group tolerant. The application of this suite of allylation reactions to the catalytic asymmetric synthesis of natural products is an ongoing topic of research in our laboratory.[24,31]

To further demonstrate the utility of these products, we transformed ketone (*S*)-**9** into several familiar cyclic frameworks (Scheme 9a). Wacker oxidation of (*S*)-**9** followed by aldol condensation gave enone **52** in good yield. Another functionalized [6,5] skeleton was formed in a three-step sequence by olefin cross metathesis with methyl vinyl ketone catalyzed by the Grubbs second-generation Ru complex (**53**),[76] olefin hydrogenation, and aldol condensation under basic conditions to afford exocyclic enone **54**. Carbocyclic [6,6] ring systems were accessible as well; multi-step elaboration of the allyl group afforded an intermediate diketone, which underwent aldol condensation to form enone **55** in



Scheme 9. Useful derivatives of enantioenriched cyclic ketones.[27a,c] i) $PdCl_2$, O_2, $Cu(OAc)_2{\cdot}H_2O$, dimethylacetamide (DMA), H_2O; ii) KOH, EtOH, 60–80 °C; iii) **53**, methyl vinyl ketone (MVK), CH_2Cl_2, 40 °C; iv) H_2, Pd/C, EtOAc; v) KOH, EtOH, 65 °C; vi) ethylene glycol, pyridinium *para*-toluenesulfonate (PPTS); vii) $BH_3{\cdot}THF$, $NaBO_3{\cdot}4H_2O$; viii) $(COCl)_2$, DMSO, Et_3N; ix) MeMgBr, THF; x) $(COCl)_2$, DMSO, Et_3N; xi) $TsOH{\cdot}H_2O$, acetone, H_2O; xii) KOH, EtOH, 60 °C; xiii) peracetic acid, Na_2CO_3, CH_2Cl_2, 0–25 °C; xiv) **53** (3 mol%), CH_2Cl_2, 40 °C; xv) ethylene glycol, PhH, Dean–Stark; xvi) O_3, CH_2Cl_2, −78 °C then Me_2S; xvii) KOH, EtOH, 75 °C; xviii) $TsOH{\cdot}H_2O$, MeOH; xix) H_5IO_6, THF/H_2O; xx) CH_3I, K_2CO_3, DMF; xxi) O_3, MeOH, −78 °C then Na_2SO_3.

42% overall yield. Enone **55**, which has been classically produced by Robinson annulation, has been used extensively in organic synthesis.[77] As a final transformation of (*S*)-**9**, we performed a Baeyer–Villiger oxidation with peracetic acid to give caprolactone **56**. This transformation demonstrates the conversion of our enantioenriched quaternary stereocenter into a latent tertiary alcohol with defined absolute stereochemistry and entry into acyclic systems.

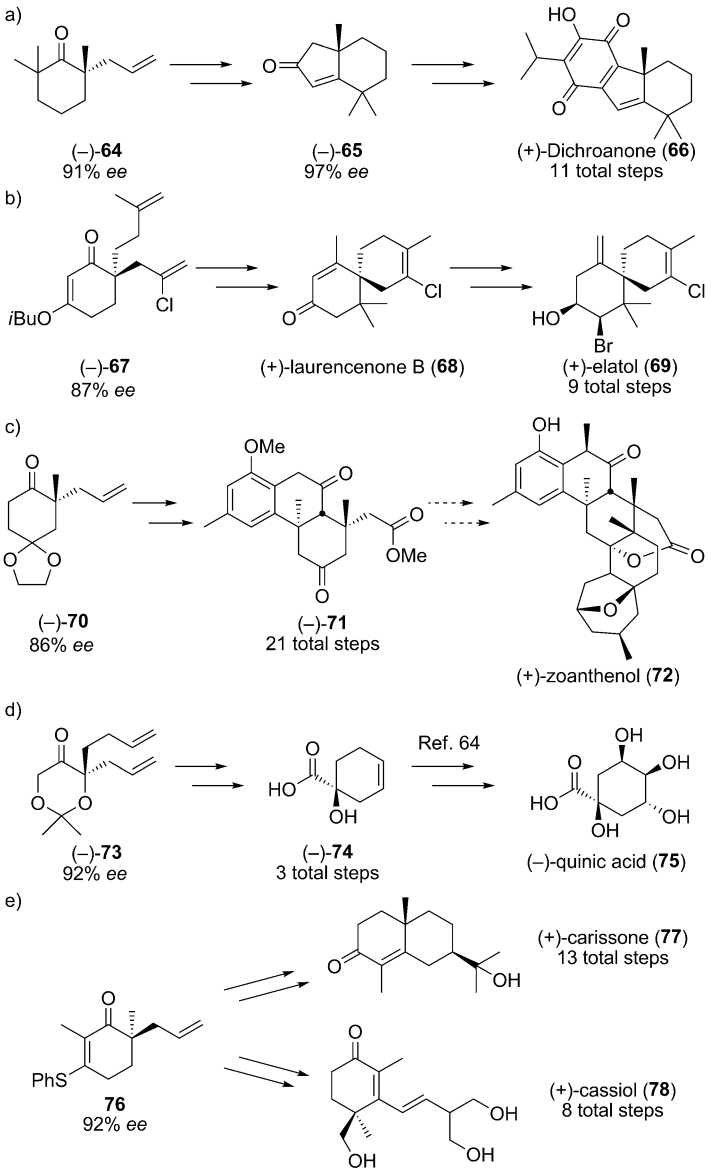
Carbocyclic spiro compounds represent a particularly challenging subclass of quaternary stereocenters. To complement the syntheses of fused cyclic skeletons above, allyl

methallyl ketone **57** was used for the synthesis of ring systems containing spiro quaternary stereocenters. Ketone **57** could be treated with the Grubbs second-generation catalyst (**53**)[76] in dichloromethane to give a good yield of spiro-[4.5]ketone **58** (Scheme 9b). Spiro[5.5]enone **59** was produced in modest yield by treatment of ketone **57** with standard ketal protection conditions, followed by ozonolysis, and exposure to a base (Scheme 9c).

The dioxanone class of substrates provided routes to other important derivatives (Scheme 9d). Cleavage of the acetal with *para*-toluenesulfonic acid generated dihydroxy ketones (e.g., **60**→**61**). These dihydroxy ketones underwent selective oxidative cleavage upon exposure to periodic acid and after esterification the corresponding hydroxyesters were isolated (e.g., **62**). Overall yields for the transformation from dioxanone to the hydroxyester (**60**→**62**) were 41–81% for three steps. In the case of chlorinated compound **62**, subsequent ozonolysis formed citramalic acid dimethyl ester (**63**), which was correlated to literature data to establish the absolute configuration of dioxanone (−)-**60** to be *S*.[78]

Similar tactics have enabled the use of the enantioselective Tsuji alkylation in a number of synthetic efforts.[24,31] Ketone (*S*)-**64** (Scheme 10a) was readily converted into enone **65**, which could be recrystallized via the semicarbazone derivative to 97% *ee*. Enantioenriched enone **65** was then elaborated to the antipode of the natural product dichroanone (**66**) in seven additional steps.[24a] A strategy comprising enantioselective allylation and ring-closing metathesis was employed to synthesize the spirocyclic natural product elatol (**69**) and the purported structure of laurencenone B (**68**) from vinylogous ester **67** (Scheme 10b).[24c,31] Ongoing attempts to prepare the marine alkaloid zoanthenol (**72**) feature α-quaternary ketone **70** as a key synthon for the preparation of the ABC tricyclic substructure (**71**) of the target molecule (Scheme 10c).[24b] Dioxanone **73** was converted into cyclohexane **74** in three steps and 50% yield (Scheme 10d). Hydroxy acid **74** has previously been employed in the synthesis of quinic acid (**75**),[79] a common chiral pool starting material used in many synthetic routes,[80] including the total synthesis of dragmacidin F reported by our laboratory.[81] Vinylogous ester **76** is a versatile precursor and can be elaborated into the natural products carissone (**77**)[24e] and cassiol (**78**).[24f]

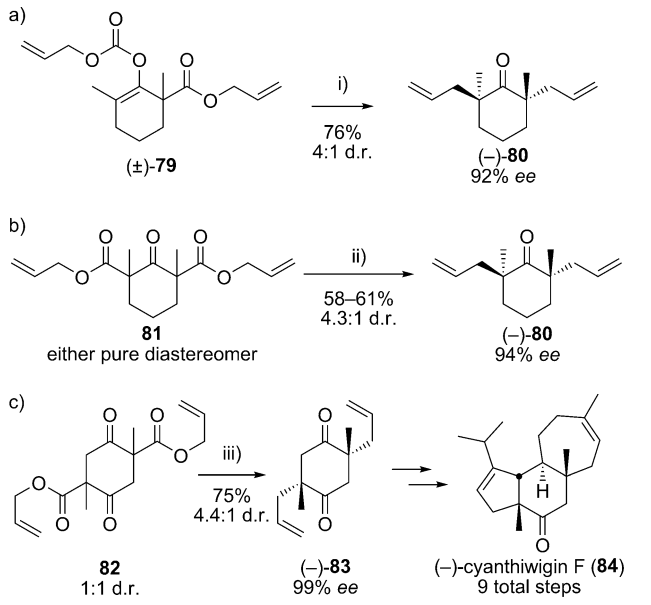
In an effort to construct more than one quaternary stereocenter in a single transformation, we designed substrate **79** (Scheme 11a), which contains a latent allyl β-ketoester moiety to be revealed by the reaction of the allyl enol carbonate portion of the molecule. To our delight, a cascade allylation occurred to afford C_2-symmetric ketone **80** as the predominant product in 92% *ee* with 4:1 d.r. Similarly, bis(β-ketoester) substrates may be employed in a stereoconvergent process during which each of the three stereoisomeric starting materials (i.e., two C_2 symmetric enantiomers and one meso diastereomer) are converted into enantioenriched products with excellent stereocontrol (e.g., **81**→**80**, Scheme 11b and **82**→**83**, Scheme 11c). We have successfully employed this double enantioselective decarboxylative allylation strategy in the total synthesis of the cyathin diterpenoid cyanthiwigin F (**84**, Scheme 11c).[24d]



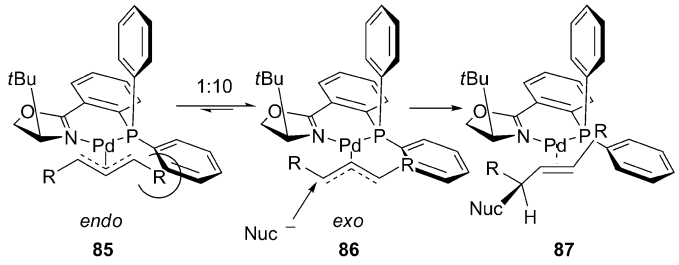
Scheme 10. Enantioenriched cyclic ketones in the synthesis of natural products.[24,27c]

Mechanistic insights: Although we have not fully elucidated the fine mechanistic details of the enantiodiscrimination with the Pd–PHOX catalyst system, an intriguing picture of the reaction's general mechanism has emerged from our experimental studies. A number of experimental observations suggest that the mechanism of our allylation of prochiral nucleophiles differs substantially from that of the Pd–PHOX-catalyzed malonate alkylation of prochiral allyl fragments, which has been studied in detail by the groups of Helmchen[82a–d] and Pfaltz.[82e]

The model described by Helmchen and co-workers for the asymmetric allylic alkylation of prochiral allyl electrophiles (R≠H, Scheme 12) with Pd–PHOX catalysts involves



Scheme 11. Enantioselective cascade allylations generating two quaternary centers.[27b,24d] i) (*S*)-**19** (10 mol%), $[Pd_2(dba)_3]$ (4 mol%), THF, 40°C, 6 h; ii) (*S*)-**19**, $[Pd_2(pmdba)_3]$ (pmdba = di(*para*-methoxybenzylidene)acetone), THF, 25°C; iii) (*S*)-**19**, $[Pd(dmdba)_2]$, Et_2O.

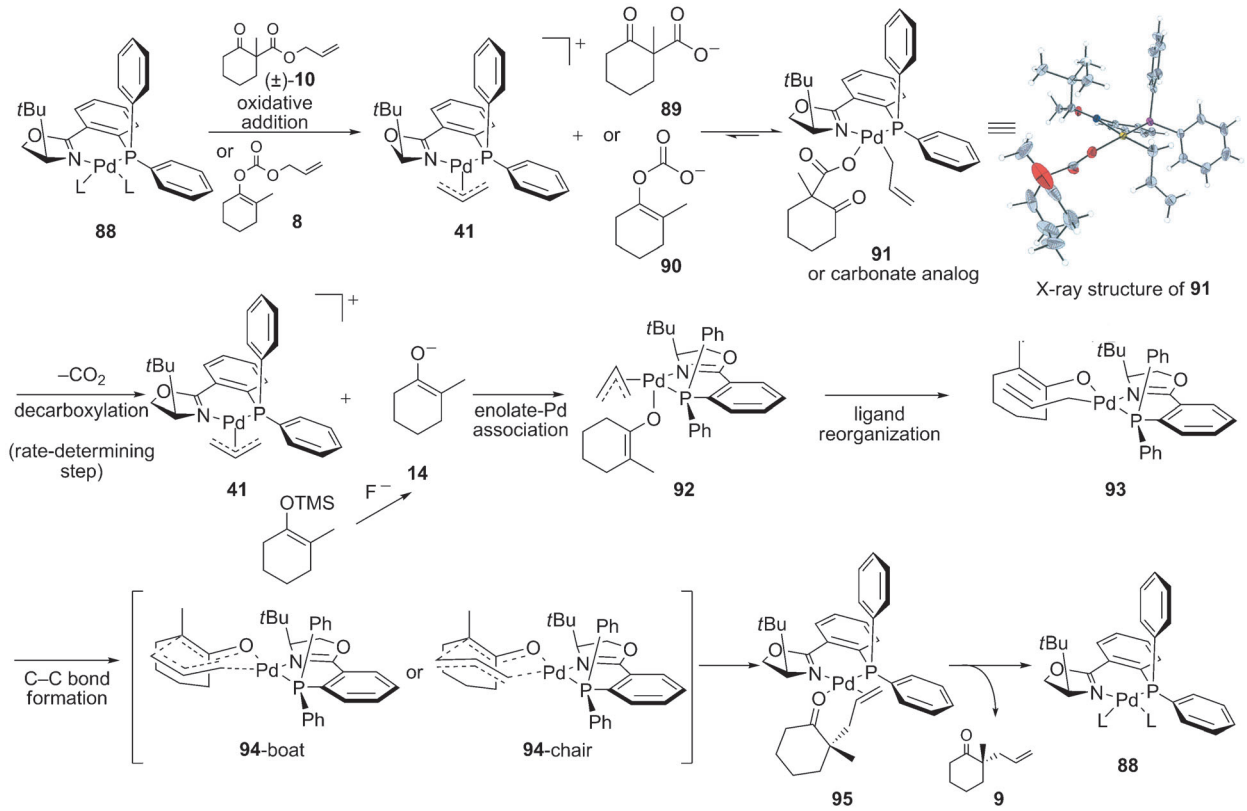


Scheme 12. Helmchen's outer-sphere mechanism for asymmetric allylation of prochiral allyl electrophiles.

attack at one allyl terminus of a (PHOX)Pd–π-allyl complex by an outer-sphere malonate anion. The allyl group isomers **85** and **86** are in rapid equilibrium such that the nucleophile's preferred attack (**86**), from the open quadrant at the allyl terminus *trans* to phosphorus, is nearly the exclusive reaction pathway. The resulting Pd^0–olefin complexes (e.g., **87**) have been observed by low temperature NMR spectroscopy.[82a,b] Notably, stereoinduction in these alkylation reactions suffered if the steric bulk of the allyl substituents was reduced (e.g., 96% *ee* for R = *i*Pr and 71% *ee* for R = Me).[83] It was difficult to rationalize the high levels of stereoinduction observed in our allylation by this outer-sphere mechanism because our substrates typically have unsubstituted allyl termini. Additionally, the formation of the new stereocenter on the enolate through an outer-sphere mechanism would require the chiral Pd complex to differentiate between the prochiral faces of an unassociated enolate, for which steric and electronic interactions between the nucleophile and the distant chiral backbone would be minimal.[84] Moreover, a gearing effect through the allyl ligand is unlikely given the lack of sterically large groups (R = H).

In addition to these hypothetical arguments, we have made several experimental observations that do not correlate well with an outer-sphere enolate attack mechanism. The high enantioselectivity under our conditions appears to correspond with circumstances that would keep ion pairs tightly associated. The range of effective solvents found during our optimization studies demonstrated this trend; ethereal solvents (e.g., THF), aromatic solvents (e.g., benzene), ethyl acetate, and triethylamine share few properties other than having low dielectric constants in the range 2–8, but each provided products in high *ee* (see Table 3). In media with such low dielectric constants, dissociative solvation of ion pairs is difficult.[85] In conjunction with the lack of other counterions in the reaction, the low dielectric value would tend to enforce an inner-sphere mechanism wherein close contact of the enolate and the chiral environment would facilitate discrimination between the prochiral enolate faces.[86]

Based on our initial reasoning and empirical observations, we have developed a working model for the course of the reaction through an inner-sphere mechanism (Scheme 13). Oxidative addition of Pd^0–PHOX complex **88** to substrate **8** or **10** leads to [Pd(allyl)PHOX] complex **41** and carboxylate **89** or mixed carbonate **90**. We believe that an equilibrium exists between the charge-separated form and the coordination complex bearing an η^1-allyl group (e.g., **91**). We have isolated and characterized β-ketocarboxylate analogue **91** by X-ray crystallography and found that it can decompose to deliver enantioenriched ketone **9**, and therefore appears to be an important intermediate along the reaction pathway.[87] Subsequent loss of CO_2, which is most likely Pd-assisted, leads to enolate **14** and Pd complex **41**. Association of these two fragments leads to five-coordinate intermediate **92**, a compound resembling a transition state for associative substitution with the enolate bound to the sterically less-encumbered apical position of the square-planar metal. By slightly different means, allyl enol carbonate and silyl enol ether substrates may intercept the key structure **92**. Shifting of the allyl group from an η^3- to an η^1-binding mode allows the enolate fragment to move into the square plane and form intermediate **93**, thus completing the associative ligand substitution. From this complex, a standard three-centered reductive-elimination pathway would require a shift from an *O*- to a *C*-bound Pd enolate.[88] Although possible, we reasoned that this isomerization would be unfavorable due to the steric demands of the resulting tertiary palladium species. As an alternative, we postulated an extended reductive-elimination pathway proceeding through a cyclic seven-membered pericyclic transition state (**94**-boat or **94**-chair) similar to a sigmatropic rearrangement.[89,90] Importantly, situating the carbocyclic ring of the enolate fragment away from the bulky *t*Bu group of the oxazoline provides a plausible predictive model for the observed absolute enantiofacial selectivity.[37] Liberation of the product ketone (**9**) from complex **95** regenerates catalytic Pd^0 species **88**.



Scheme 13. Proposed inner-sphere mechanism for asymmetric alkylation of prochiral enolate nucleophiles.

Typically, inner- and outer-sphere processes may be differentiated by stereochemically labeling the allyl fragment and evaluating the relative stereochemistry of the products.[91] For example, this type of study was carried out by Trost and co-workers on their decarboxylative allylic alkylation system and the results suggest an outer-sphere mechanism.[42k] However, in this case, these experiments could not be performed because the necessary cyclic carbonates suffered from very poor reactivity and enantioselectivity. In fact, even simple substitution of the termini of acyclic allyl groups (e.g., crotyl carbonates) severely impacts reactivity and perhaps suggests that for such substrates a different mechanism operates.[92] Given these substrate limitations, we were obliged to seek other forms of mechanistic evidence to evaluate our proposal.

Because it is conceivable that multiple ion pairs could be involved in the transition state (e.g., an enolate bound to one {Pd(allyl)PHOX} fragment could attack the Pd-bound allyl fragment associated with another enolate), we conducted simple kinetics experiments that support a pathway involving a single metal center (Figures 1–4).[53] Initial attempts to examine the kinetics of the reaction with respect to the Pd–PHOX complex did not give clear results. We suspect that the precision of the calculated initial rates may be complicated by inconsistent aerobic oxidation of the phosphine ligand,[32] leading to some uncertainty in the effective catalyst concentration. A fit to a first-order rate law with respect to Pd–PHOX concentration is most consistent with the experimental observations, tentatively supporting the notion that a single metal center is involved in the mechanism (Figure 1). Additionally, the lack of an observed nonlinear effect between product and ligand *ee* is also consistent with the action of a single metal center in the enantiodetermining step (Figure 2).[93] Interestingly, kinetic studies also found a zero-order dependence on substrate concentration in the allyl enol carbonate (Figure 3) and β-ketoester (Figure 4) cases.[94] Based on these results, we suspect that the rate-limiting step is either loss of CO_2 from a Pd–carboxylate intermediate (e.g., **91**→**41**+**14**, Scheme 13), or C–C bond formation (e.g., **93**→**95**, Scheme 13). The isolation of relatively stable Pd–carboxylate complex **91** is indicative of a slow decarboxylation step. The longer reaction times observed with β-ketoester substrates compared with those of the corresponding allyl enol carbonates is also more consistent with decarboxylation as the rate-determining step because the rate difference would be attributed to the difference in breaking a C–C bond (β-ketoester) compared to a C–O bond (enol carbonate). However, we cannot rule out the possibility that different substrate classes may have different rate-determining steps.

In addition to these studies, we designed other experiments to differentiate our proposed mechanism from that elucidated by Helmchen and co-workers.[82] Enolates in which charge is delocalized (e.g., those derived from

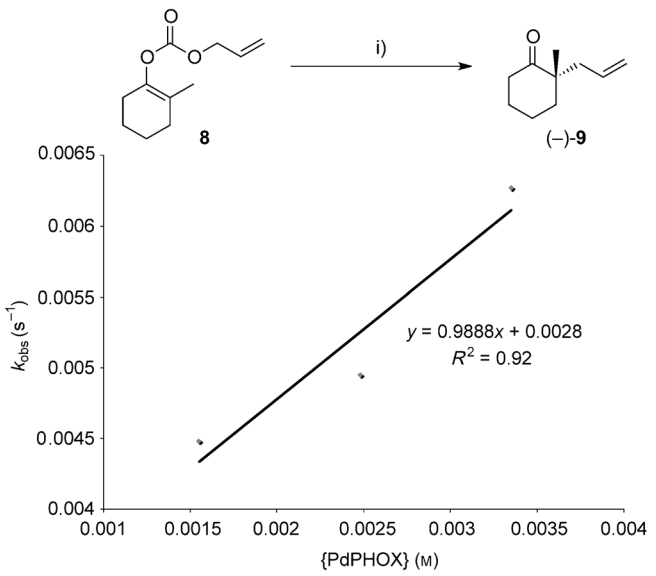


Figure 1. Plot of k_{obs} versus concentration of the [Pd(PHOX)] complex for an allyl enol carbonate. i) [$Pd_2(dba)_3$] (X mol%), (S)-*t*Bu-PHOX (2.5X mol%), THF (0.03 M), 25° C, tridecane internal standard (0.15 mmol), 0.3 mmol scale.

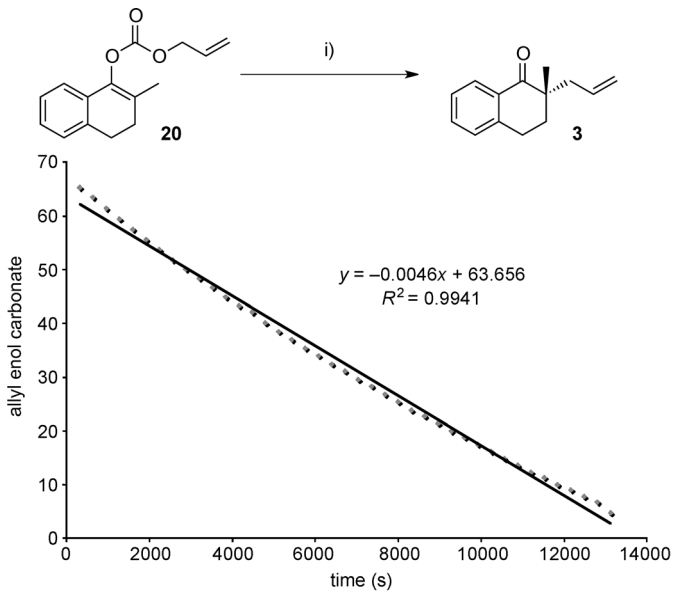


Figure 3. Plot of allyl enol carbonate ^{1}H NMR integral versus time [s]. i) [$Pd_2(dba)_3$] (5 mol%), (S)-*t*Bu-PHOX (12.5 mol%), [D_8]THF (0.1 M), 0° C, 1,4-dimethoxybenzene internal standard (0.0175 mmol), 0.05 mmol scale.

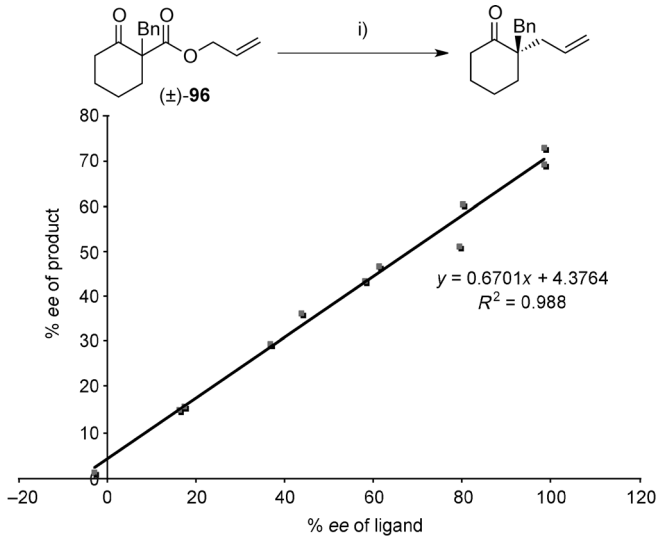


Figure 2. Plot of *i*Pr-PHOX *ee* versus product *ee*.[95] i) [$Pd_2(dba)_3$] (5 mol%), *i*Pr-PHOX (12.5 mol%), THF (0.033 M), 25° C, 0.1 mmol scale.

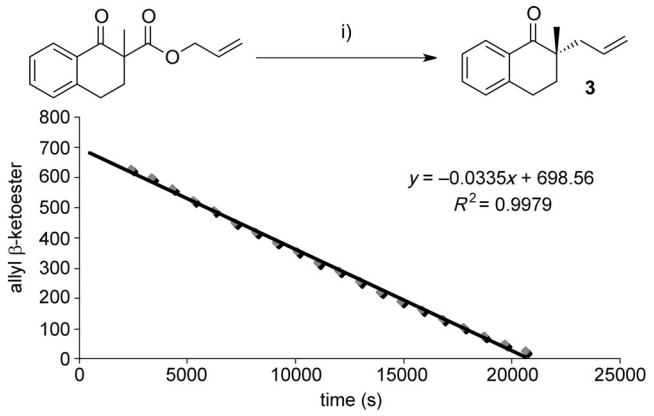
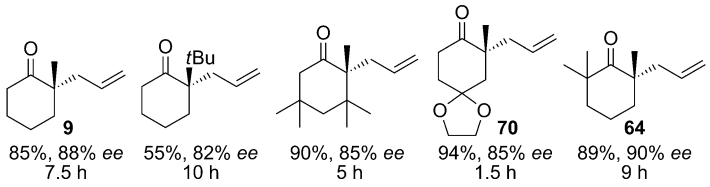


Figure 4. Plot of allyl β-ketoester ^{1}H NMR integral versus time [s]. i) [$Pd_2(dba)_3$] (5 mol%), (S)-*t*Bu-PHOX (12.5 mol%), [D_8]THF (0.1 M), 25° C, 0.05 mmol scale.

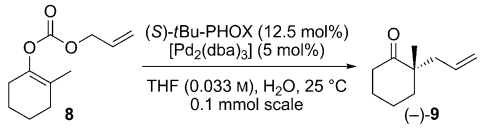
β-ketoesters or α-aryl ketones), which should tend to form weak ion pairs, give high yields but extremely low levels of enantioselectivity (see Table 16).[96] This result suggests that, in such cases, allylation proceeds primarily through the more conventional, although in this case poorly selective, outer-sphere attack. The reactivity of sterically demanding substrates in our reaction is also inconsistent with an outer-sphere, intermolecular nucleophilic enolate attack. In a nucleophilic bimolecular reaction, such as the Helmchen allylation mechanism (Scheme 12), steric bulk near the site of bond formation typically impedes the rate of reaction.[97] However, in our case there is little difference in the reaction time, yield, or enantioselectivity when comparing the formation of ketone **9** with that of more sterically demanding ketones (Scheme 14). This observation is more consistent with an intramolecular reaction mechanism.

Another observation at odds with an external attack mechanism is the unusual tolerance to water (Table 18). Multiple equivalents of water introduced into the reaction have only a moderate effect on the yield of the reaction. This contrasts with typical enolates, which are rapidly quenched by water even at low temperatures, and suggests that once decarboxylation occurs the intermediate enolate



Scheme 14. Comparison of sterically varied products formed at 25 °C in THF.

Table 18. Effect of water on asymmetric alkylation.[a]

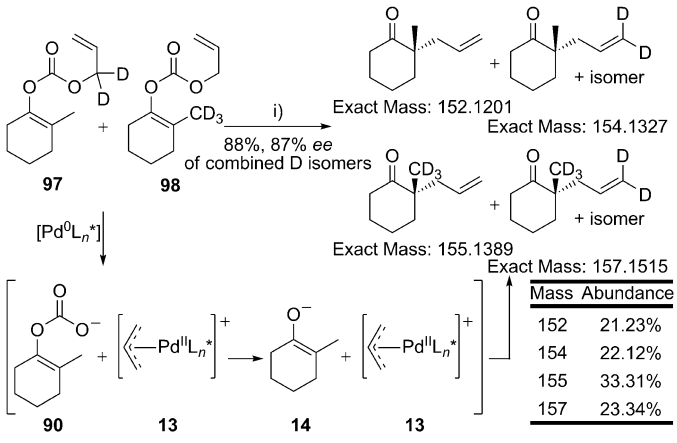


	H_2O added [equiv][b]	Yield [%][c]	*ee* [%][d]
1	0	95	86
2	0.55	99	87
3	1.64	88	84
4	8.25	70	61
5	16.5	67	49
6	33.3	63	40

[a] Data reported are the average of three experiments. [b] H_2O added after Pd/PHOX complexation, but before the substrate. [c] GC yield relative to an internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC.

formed in the reaction is tightly associated with or covalently bound to its Pd counterion for most of its lifetime.[98]

In an effort to trace the fate of the allyl and enolate fragments in the course of the reaction, we performed crossover experiments with a 1:1 mixture of deuterated allyl enol carbonates **97** and **98** in THF, dioxane, and benzene (Scheme 15).[99] Analysis of the products by high-resolution mass spectrometry revealed the presence of all four possible product masses in nearly equal amounts.[100] In conjunction with the water addition experiments, this observation suggests that a palladium enol carbonate species (**41**+**90** or **41**·**90**) may be a long-lived intermediate. Such an intermedi-



Scheme 15. Crossover experiments with deuterated allyl enol carbonates.[27b] i) $[Pd_2(dba)_3]$, (*S*)-*t*Bu-PHOX, THF, 25 °C, 2 h.

ate would not be readily protonated by water,[101] and this delocalized anion may facilitate crossover by dissociation from the metal center. In the case of β-ketoester substrates, a β-ketocarboxylate intermediate (e.g., **91**) may play an analogous role.[102]

To validate our hypothesis regarding the persistence of an intermediate carboxylate or mono-alkyl carbonate (**89** or **90**, respectively), we collected ^{31}P NMR data during the reaction.[27d,53] Non-ligated *t*Bu-PHOX (**19**) exhibited a ^{31}P resonance at −5.9 ppm. If $[Pd_2(dba)_3]$ and *t*Bu-PHOX were complexed, a new resonance was observed at 18.8 ppm along with excess ligand (Figure 5a). If substrate (±)-**10** was added, the resonance at 18.8 ppm disappeared immediately and the only observed intermediate was found at 30.9 ppm, which persisted until the end of the reaction (Figure 5b). If the substrate was completely consumed, the initial Pd–PHOX complex returned at 18.8 ppm (Figure 5c).[103] Inter-

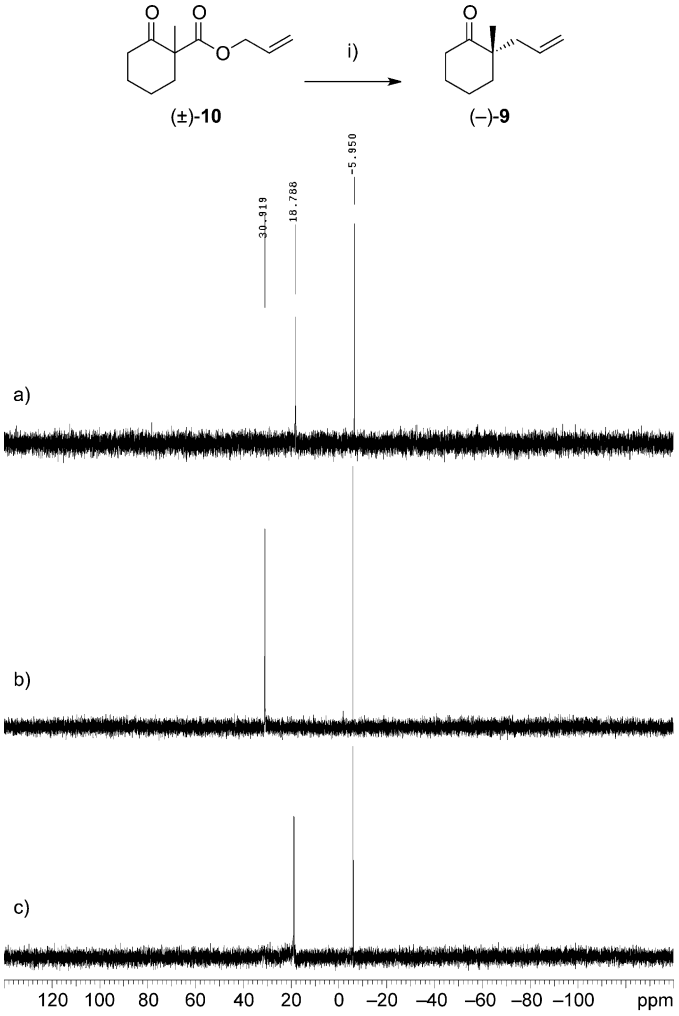


Figure 5. ^{31}P NMR spectra collected during the enantioselective allylation reaction: a) [(PHOX)Pd(dba)] complex (18.8 ppm)[27d] and excess PHOX ligand (*S*)-**19** (−5.9 ppm) prior to addition of substrate; b) after addition of substrate (±)-**10** during the reaction (carboxylate **91** is observed at 30.9 ppm); and c) after complete consumption of the substrate. i) (*S*)-**19**, (14 mol%), $[Pd_2(dba)_3]$ (5 mol%), THF.

estingly, similar behavior was observed in reactions with allyl carbonates, although the chemical shifts of the intermediate species differed slightly.

The separately prepared $[Pd^{II}(allyl)(PHOX)]^+[PF_6]^-$ complex (**41**, Scheme 5) exhibited two ^{31}P resonances (other than those due to PF_6^-) at 23.5 and 22.5 ppm in a 2:1 ratio (in THF), due to the mixture of *endo*- an *exo*-allyl isomers.[82] The different chemical shifts for this Pd^{II} complex than those observed during the reaction suggest a different ligation environment about the Pd center. To correlate these two different species, nBu$_4$NOAc was added to a solution of $[Pd^{II}(allyl)(PHOX)]^+[PF_6]^-$, and a new species was observed at 30.9 ppm, which matches that of the independently synthesized $[Pd^{II}(allyl)(PHOX)(OAc)]$ complex.[27d] Based on these experiments, we believe that the observed catalyst resting state in solution is likely the $[Pd^{II}(allyl)(PHOX)]^+$/[carboxylate]$^-$ ion pair (**41**+**89**, Scheme 13) or coordination complex **91**. Efforts to fully characterize additional intermediate structures are ongoing.

The solid-state structure of the independently prepared $[Pd^{II}(allyl)PHOX]^+[PF_6]^-$ salt (**41**) lends credence to the possibility of an apically bound palladium enolate. As shown in Scheme 5, after recrystallization the complex partially co-crystallizes with a molecule of ethanol in its unoccupied quadrant.[47] We envision that this is the likely site of enolate coordination (e.g., apically bound enolate complex **92**, Scheme 13).

Given the body of evidence accrued in these experimental studies and our inability to probe the mechanism through classical stereochemical labeling experiments,[91] we initiated a collaboration with the Goddard group at Caltech to investigate the details of the mechanism through computational modeling.[75] The computational studies carried out have corroborated our initial hypothesis regarding the inner-sphere mechanism, the difficult isomerization between the *O*- and *C*-bound Pd enolates, and the unusual cyclic seven-membered reductive-elimination pathway (Scheme 13). Notably, these calculations have found that the traditional outer-sphere mechanism (Scheme 12) is significantly higher in energy than the inner-sphere pathway. The simulations have not yet elucidated the fine details of the origin of the enantioselectivity. Experiments and computational studies to better characterize the reaction mechanism are under way with the hope of improving the enantioselectivity and scope of the asymmetric alkylation.

Conclusion

To address a significant deficiency in the asymmetric alkylation literature, we have developed a strategy to prepare enantioenriched cycloalkanones in high yield. This work provides direct routes to valuable enantioenriched α-quaternary ketones from readily accessible enolate precursors. Critical to our success was the use of enolate precursors, which can be converted into enolates under mild conditions, and the use of a chiral catalyst that exhibited the enolate isomeric fidelity found in Tsuji's non-enantioselective system. The reactivity and enantioselectivity of the alkylation reactions have proven to be quite general with respect to substrate steric bulk, ring size, unsaturation, and diverse functional groups. We have demonstrated the relevance of the α-quaternary ketones produced in the reaction by their conversion into a number of carbocyclic chiral building blocks, including several spiro motifs, as well as in the asymmetric syntheses of several natural products. Studies directed toward further development of the scope of this reaction and catalyst system are ongoing. Additionally, the continued application of our asymmetric alkylation as a key enantiodetermining step in natural product synthesis will be reported in due course.

Experimental Section

Representative procedure for the enantioselective decarboxylative alkylation of allyl enol carbonates: A round-bottom flask (50 mL) equipped with a magnetic stirring bar was flame dried under vacuum. After cooling under dry argon, $[Pd_2(dba)_3]$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*Bu-PHOX (**19**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time allyl enol carbonate **8** (196.2 mg, 1.0 mmol, 1.0 equiv) was added by syringe in one portion. When the reaction was complete by TLC (2 h), the reaction mixture was dried under reduced pressure, and the residue purified by chromatography (2→3% Et_2O in pentane on SiO_2) to afford (*S*)-2-allyl-2-methylcyclohexanone ((*S*)-**9**; 129.6 mg, 85.1%, 87% *ee*) as a colorless oil. $[\alpha]_D^{21} = -49.64$ ($c = 2.38$ in hexane, 98% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.75$–5.61 (m, 1H), 5.05 (s, 1H), 5.01–4.99 (m, 1H), 2.40–2.31 (m, 3H), 2.21 (dd, $J = 13.8$, 7.5 Hz, 1H), 1.90–1.65 (m, 5H), 1.63–1.50 (m, 1H), 1.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 215.4$, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4, 22.6, 21.0 ppm; IR (neat film NaCl): 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{10}H_{16}O^+$: 152.1201 $[M]^+$; found: 152.1204.

Representative procedure for the enantioselective decarboxylative alkylation of silyl enol ethers: A round-bottom flask (50 mL) equipped with a magnetic stirring bar was flame dried under vacuum. After cooling under dry argon, $[Pd_2(dba)_3]$ (22.9 mg, 0.025 mmol, 0.025 equiv), (*S*)-*t*Bu-PHOX (**19**, 24.2 mg, 0.0625 mmol, 0.0625 equiv), and TBAT (189 mg, 0.35 mmol, 0.35 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time diallyl carbonate (150.6 μL, 1.05 mmol, 1.05 equiv) and silyl enol ether **SI23** (see the Supporting Information; 184.35 mg, 1.0 mmol, 1.0 equiv) were added sequentially by syringe in single portions. When the reaction was complete by TLC (2 h), the reaction mixture was dried under reduced pressure, and the residue purified by chromatography (2→3% Et_2O in pentane on SiO_2) to afford ketone (*S*)-**9** (144.3 mg, 94.8%, 87% *ee*).

Representative procedure for the enantioselective decarboxylative alkylation of β-ketoesters: A round-bottom flask (100 mL) was equipped with a magnetic stirring bar and flame dried under vacuum. After cooling under dry nitrogen, $[Pd_2(dba)_3]$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*Bu-PHOX (**19**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry nitrogen. Dry THF (30 mL) was then added and the resulting solution stirred at 25 °C for 30 min. At this point, allyl 1-methyl-2-oxocyclohexanecarboxylate ((±)-**10**) was added through a syringe in one portion. When the reaction was complete by TLC (7.5 h), the reaction mixture was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, 1.5→2.5% Et_2O in pentane) to afford ketone (*S*)-**9** (129.6 mg, 85%, 88% *ee*).

Acknowledgements

This publication is based on work supported by award number KUS-11–006–02, made by the King Abdullah University of Science and Technology (KAUST). We thank the NIH-NIGMS (R01 GM080269–01 and postdoctoral fellowships to AMH and DEW), The Fannie and John Hertz Foundation (predoctoral fellowship to DCB), Eli Lilly (predoctoral fellowships to JTM, RMM, and MRK), Ono Pharmaceutical Co., Ltd. (postdoctoral fellowship to KT), The Hungarian–American Enterprise Scholarship Fund (postdoctoral fellowship to ZN), Takeda Pharmaceutical Co., Ltd. (postdoctoral fellowship to MS), The California Tobacco-Related Disease Research Program of the University of California (predoctoral fellowship to JLR, grant number 14DT-0004), Marcella R. Bonsall and the Dalton Fund (undergraduate fellowships to SRL), the Caltech Amgen Scholars Program (undergraduate fellowship to KVP), The 21st Century COE Program for Frontiers in Fundamental Chemistry from the Ministry of Education, Culture, Sports, Science and Technology, Japan (financial support to AI), the A. P. Sloan Foundation, Research Corporation, the Dreyfus Foundation, Bristol–Myers Squibb, GlaxoSmithKline, Johnson and Johnson, Amgen, Merck Research Laboratories, Pfizer, Novartis, Roche, Abbott Laboratories, Boehringer–Ingelheim, AstraZeneca, and Caltech for financial support. We acknowledge Dr. Mike Day and Larry Henling for assistance with X-ray crystallography. Ruthenium olefin metathesis catalysts were generously donated by Materia.

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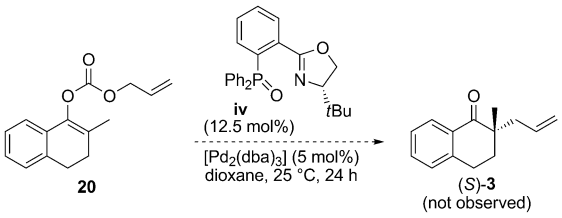
[31] The rate and selectivity of the reaction are typically unchanged when Pd^0 sources other than $[Pd_2(dba)_3]$ are used (e.g., bis[di(3,5-dimethoxybenzylidene)acetone]palladium(0) ($[Pd(dmdba)_2]$) and tris[di(4-methoxybenzylidene)acetone]dipalladium(0) ($[Pd_2(pmdba)_3]$)). For a case in which the choice of Pd^0 source affected conversion, see: D. E. White, I. C. Stewart, B. A. Seashore-Ludlow, R. H. Grubbs, B. M. Stoltz, *Tetrahedron* **2010**, *66*, 4668–4686; for a discussion of the utility of $[Pd(dmdba)_2]$ and $[Pd_2(pmdba)_3]$, see Ref. [48].

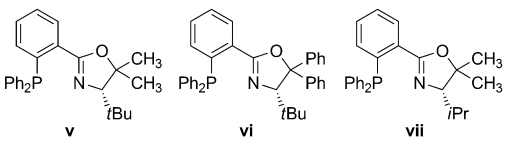
[32] We have studied the ^{31}P NMR spectra of the reaction at length (see Figure 5 and the Supporting Information), and we believe that phosphine oxide **iv** is produced as a catalyst decomposition product when O_2 is present. In the absence of Pd, PHOX ligand **19** does not oxidize significantly in the solid state or in solution. Phosphine oxide **iv** may be observed during the reaction by ^{31}P NMR spectroscopy (27 ppm) in typical benchtop experiments. Typically, the rate of ligand oxidation is slow relative to the time frame of the decarboxylative alkylation (< 12 h), and reactions may be carried out routinely on the benchtop under inert atmosphere in dry, degassed solvents. Substrates that are particularly slow to react are often more efficiently converted to products in a glovebox to extend the lifetime of the catalyst (Figure 5 shows virtually no ligand oxidation occurs if the reaction is rigorously protected from air). We have independently synthesized (*S*)-*t*Bu-PHOX oxide (**iv**) and found that if used as a ligand for the conversion of tetralone-derived allyl enol carbonate **19** into ketone **3** no reaction was observed.



[33] As a result of our desire to generate a large variety of PHOX ligands, we adapted a procedure for C–P bond formation disclosed by Buchwald and co-workers for the synthesis of PHOX ligands, see: a) K. Tani, D. C. Behenna, R. M. McFadden, B. M. Stoltz, *Org. Lett.* **2007**, *9*, 2529–2531; b) M. R. Krout, J. T. Mohr, B. M. Stoltz, *Org. Synth.* **2009**, *86*, 181–193; c) D. Gelman, L. Jiang, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 2315–2318; d) for an alternative cross-coupling with phosphine oxides, see: N. T. McDougal, J. Streuff, H. Mukherjee, S. C. Virgil, B. M. Stoltz, *Tetrahedron Lett.* **2010**, *51*, 5550–5554.

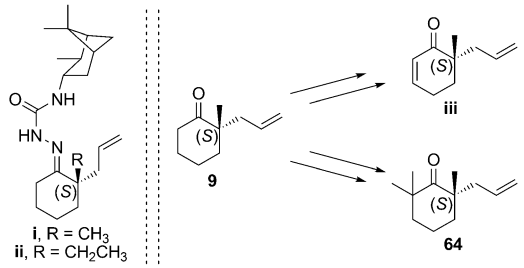
[34] Synthesized in analogy to PHOX ligands prepared by Helmchen and co-workers, see Ref. [29c].

[35] Additionally, we have prepared the similar ligands **v** and **vi**. In our prototypical reaction (**8**→**9**), the product was formed in 86 and 79% *ee* , respectively, with complete substrate conversion. A recent publication from another laboratory has put forth related ligand **vii**, which can be synthesized from valine, as an alternative to *t*Bu-PHOX. The authors report comparable levels of enantioinduction with fluorinated enol silane substrates; see: É. Bélanger, M.-F. Pouliot, J.-F. Paquin, *Org. Lett.* **2009**, *11*, 2201–2204.



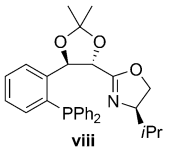
[36] B. Wiese, G. Helmchen, *Tetrahedron Lett.* **1998**, *39*, 5727–5730.

[37] a) To definitively assign the absolute stereochemistry of the newly formed quaternary stereocenter, we prepared the corresponding semicarbazones **i** and **ii**, each bearing an isopinocampheylamine portion of known configuration, which were then characterized by X-ray crystallography. In addition, we converted ketone **9** into cycloalkanones **iii** and **64**, which matched the major enantiomer of



products formed in the direct allylation reactions (see the Supporting Information for details). The *S* configuration of tetralone **3** was confirmed by comparison with literature data (see Ref. [16b]). Based on the consistent sense of enantiofacial selectivity, the stereochemistries of the remaining allylation products are inferred by analogy; b) the recrystallization of semicarbazone derivatives as a means to increase the *ee* of our products has proven to be of general use with the α-quaternary ketones and their derivatives; for an example, see: Ref. [24a]; c) for an optimized procedure for the preparation and recrystallization of the semicarbazone (a single recrystallization from toluene provided material of 98% *ee*), see: J. T. Mohr, M. R. Krout, B. M. Stoltz, *Org. Synth.* **2009**, *86*, 194–211.

[38] Trudeau and Morken synthesized PHOX-like ligand **viii**, as well as some structurally related ligands. These were tested in a decarboxylative alkylation with carbonate substrate **20**, providing ketone **3** in up to 59% *ee*; see: S. Trudeau, J. P. Morken, *Tetrahedron* **2006**, *62*, 11470–11476.



[39] These reactions were carried out before the optimal solvent and concentration (THF at 0.031 M) were determined. We believe that reexamining these reactions under the optimized reaction conditions would not significantly change the outcome, as only increases in *ee* and yield would be anticipated.

[40] G. J. Dawson, C. G. Frost, C. J. Martin J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.* **1993**, *34*, 7793–7796.

[41] S. P. Smidt, F. Menges, A. Pfaltz, *Org. Lett.* **2004**, *6*, 2023–2026.

[42] Subsequent to our initial report on asymmetric allylation, several related reports have appeared: a) for a review, see Ref. [27g]; b) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847; c) M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem.* **2005**, *117*, 7414–7417; *Angew. Chem. Int. Ed.* **2005**, *44*, 7248–7251; d) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181; e) E. C. Burger, B. R. Barron, J. A. Tunge, *Synlett* **2006**, 2824–2826; f) B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem.* **2006**, *118*, 3181–3184; *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112; g) B. M. Trost, J. Xu, M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282–283; h) É. Bélanger, K. Cantin, O. Messe, M. Tremblay, J.-F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035; i) S. R. Schulz, S. Blechert, *Angew. Chem.* **2007**, *119*, 4040–4044; *Angew. Chem. Int. Ed.* **2007**, *46*, 3966–3970; j) É. Bélanger, C. Houzé, N. Guimond, K. Cantin, J.-F. Paquin, *Chem. Commun.* **2008**, 3251–3253; k) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357; l) Refs. [35] and [38].

[43] Reactions below 10 °C typically do not show conversion to product and are only reliably performed with highly activated substrates; for an example, see: N. T. Goodwin, Ph. D. Thesis, California Institute of Technology (USA), **2006**.

[44] Although isomerically pure enol carbonates and silyl enol ethers were desired for substrate characterization and to maximize the yield of α-quaternary ketone, it should be noted that this is not required for the allylation reaction. The less substituted enolate precursors are cleanly transformed into 2,6-substituted ketones, which are typically readily removed by chromatography and have no effect on the *ee* of the desired product.

[45] Sodium and potassium methoxide (1 equiv) could be used directly as silyl enol ether activators. However, lower yields (14 and 36%, respectively) and slightly lower *ee* values (81 and 80% *ee*, respectively) were observed.

[46] For the procedure, see: S. Liu, J. F. K. Müller, M. Neuburger, S. Schaffner, M. Zehnder, *J. Organomet. Chem.* **1997**, *549*, 283–293.

[47] $[PF_6]^-$ counterions removed for clarity. Two out of four of the crystallographically unique [Pd(allyl)PHOX] complexes in the unit cell crystallized with a molecule of ethanol. The *endo*- and *exo*-allyl isomers were present in essentially equal electron density and are modeled as a superposition of the two isomers.

[48] In some cases we have encountered difficulty in separating the cycloalkanone products from the residual dba introduced with the palladium source. As a practical consideration, it is often useful to employ bis[di(3,5-dimethoxybenzylidene)acetone]palladium(0) ([Pd(dmdba)$_2$]) or tris[di(4-methoxybenzylidene)acetone]dipalladium(0) ([Pd$_2$(pmdba)$_3$]) as the source of palladium because of the difference in polarity of dmdba and pmdba relative to dba.

[49] G. M. Coppola, H. F. Schuster, *α-Hydroxy Acids in Enantioselective Syntheses*, Wiley-VCH, Weinheim, **1997**.

[50] a) D. Enders, B. Bockstiegel, *Synthesis* **1989**, 493–496; b) D. Enders, I. Breuer, E. Drosdow, *Synthesis* **2005**, 3239–3244.

[51] For a proline-catalyzed aldol reaction with dioxanones, see: a) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235–1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212; b) for a review, see: D. Enders, M. Voith, A. Lenzen, *Angew. Chem.* **2005**, *117*, 1330–1351; *Angew. Chem. Int. Ed.* **2005**, *44*, 1304–1325.

[52] The corresponding trimethylsilyl enol ethers were relatively unstable and often could not be purified in high yield by silica gel chromatography. Comparable yield and *ee* values could be obtained if TMS enol ethers were employed in the allylation reaction. See the Supporting Information for details.

[53] See the Supporting Information for details.

[54] A. Michael, K. Wolgast, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3176–3177.

[55] For a discussion of double stereodifferentiation, see: E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 965–971.

[56] Aliquots taken during the reaction with β-ketoester (±)-**10** at 30 °C in THF show that the starting material reaches a maximum of 5% *ee* at 83% conversion for a k_{rel} of 1.1.

[57] Presumably, this is the result of cleavage of a C–C bond during decarboxylation, rather than the C–O bond found in carbonates. The exact nature of the rate-determining step of the reaction has not yet been determined.

[58] For reviews, see: a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; b) H. Stecher, K. Faber, *Synthesis* **1997**, 1–16; c) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331; d) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; e) for representative stereomutative examples, see: A. Pfaltz, M. Lautens in *Comprehensive Asymmetric Catalysis III, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, pp. 833–884; f) B. M. Trost, R. C. Bunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968–5976.

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[65] Increased enantiomeric excess was also observed with a Trost ligand derived catalyst if the central position of the allyl fragment was substituted, see: Ref. [15l].

[66] A similar increase in reactivity for vinylogous thioester substrates was observed with a Trost ligand derived catalyst, see: Ref. [42f].

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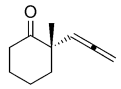

ix

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[85] For the related system by Trost and co-workers, a solvent-caged ion pair was proposed based on a lack of crossover between enolate and alkyl fragments (Ref. [42b]). However, we observed very different results from crossover experiments on our system (Scheme 15), suggesting that the details of the mechanisms of these two systems may be substantially different. In later studies (Ref. [42l]), Trost and co-workers did observe crossover in a similar experiment, although an explanation for the differing results in Ref. [42b] was not provided.

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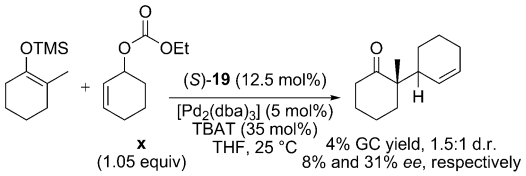

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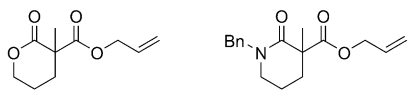
[94] We believe that the slight curvature in the data plots shown in Figures 3 and 4 are the result of catalyst decomposition during the reaction. Attempts to fit the data to higher-order polynomial expressions were not productive.

[95] For these experiments, *i*Pr-PHOX was used because of the availability of both enantiomers of valine at approximately the same cost.

[96] Substrates that would lead to highly basic enolate intermediates, such as lactone **xi** and lactam **xii**, have been problematic, presumably because decarboxylation is slow.

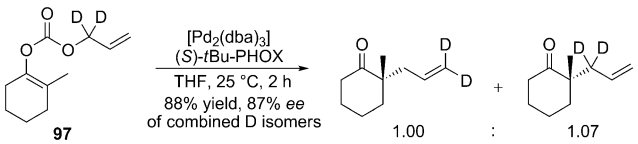


xi **xii**

[97] For example, replacement of the CH_2 group of the malonate nucleophile with CH(NHAc) increased the required reaction time from 1 h to 3–4 days; see Ref. [83].

[98] Also consistent with the presence of a Pd-bound enolate intermediate is the fact that stronger acids (e.g., formic acid) may be used to achieve an enantioselective protonation reaction. In addition, activated Michael acceptors can be employed to achieve enantioselective conjugate addition/alkylation cascades. However, empirical observations indicate that the mechanism of C–H and C–C bond formation with these alternative electrophiles differs significantly from that of C–C bond formation in the case of allyl electrophiles, see: a) Ref. [71]; b) Ref. [27e].

[99] A separate reaction with dideuterio allyl enol carbonate **97** confirms that the allyl termini are scrambled during the course of the reaction, see the Supporting Information for details.



[100] Although the total ion counts are not rigorously quantitative, they are consistent with the presence of all four masses in nearly equal proportions. The slight excess of the 155 *m*/*z* ion is likely due to the natural abundance of ^{13}C present in the dideuterio product.

[101] The pK_a of related monomethyl carbonic acid has been estimated at 2.92 (H_2O solvent, 25 °C), see: J. P. Guthrie, *Can. J. Chem.* **1978**, *56*, 2342–2354.

[102] Saegusa and co-workers suggested similar crossover pathways in a related, non-enantioselective system that uses a [Pd(PPh_3)$_4$] catalyst, see Ref. [21b].

[103] If the reaction mixture is exposed to air, *t*Bu-PHOX is cleanly converted into the corresponding phosphine oxide. Pd catalyzes this conversion. See the Supporting Information for details.

Received: November 24, 2010
Revised: July 29, 2011
Published online: November 14, 2011

