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Palladium-Catalyzed Asymmetric Allylic Alkylation of Ketone Enolates

Barry M. Trost* and Gretchen M. Schroeder[a]

Abstract: Palladium-catalyzed asymmetric allylic alkylation of nonstabilized ketone enolates to generate quaternary centers has been achieved in excellent yield and enantioselectivity. Optimized conditions consist of performing the reaction in the presence of two equivalents of LDA as base, one equivalent of trimethytin chloride as a Lewis acid, 1,2-dimethoxyethane as the solvent, and a catalytic amount of a chiral palladium complex formed from π-allyl palladium chloride dimer **3** and cyclohexyldiamine derived chiral ligand **4**. Linearly substituted, acyclic 1,3-dialkyl substituted, and unsubstituted allylic carbonates function well as electrophiles. A variety of α-tetralones, cyclohexanones, and cyclopentanones can be employed as nucleophiles. The absolute configuration generated is consistent with the current model in which steric factors control stereofacial differentiation. The quaternary substituted products available by this method are versatile substrates for further elaboration.

Keywords: allylation · asymmetric catalysis · asymmetric synthesis · palladium · quaternary stereocenters

Introduction

Alkylation of ketone enolates is a venerable reaction in organic synthesis.[1] As this transformation has proven invaluable, the development of asymmetric methods has received considerable attention.[2] Asymmetric alkylation to generate quaternary centers, that is carbon centers with four different non-hydrogen substituents, has proven particularly challenging. While significant advances toward achieving this goal have been made by the use of stoichiometric chiral auxiliaries,[3] a more attractive strategy would involve using a catalytic amount of the chirality inducing agent.[4] Catalytic asymmetric transformations benefit in terms of atom economy and require fewer chemical transformations as the chiral auxiliary is commonly installed and removed in distinct steps.[5]

Transition metal catalyzed asymmetric allylic alkylation (AAA reaction) has been shown to be an effective method for the synthesis of quaternary substituted carbon centers. The catalytic cycle consists of four steps: coordination of the transition metal to the olefin of the electrophile, ionization of the allylic leaving group to generate a π-allyl transition metal complex, alkylation by the nucleophile to generate a new transition metal olefin complex, and finally decomplexation which gives the product and returns the transition metal so that it can re-enter the cycle. When this reaction is performed in the presence of chiral ligands, asymmetric induction can potentially be achieved at the electrophile and/or at the nucleophile. Enantioselectivity at the electrophile has been extensively studied, however, enantioselectivity at the nucleophile has received far less attention. In order for chiral ligands to effect stereochemical control in a Pd-catalyzed reaction, they must influence bond-making and bond-breaking events occurring outside the coordination sphere of the metal. Discrimination of the enantiotopic faces of the nucleophile is especially difficult because the nucleophile is segregated from the chiral environment by the π-allyl moiety (Figure 1).

The first example in which a prochiral nucleophile was employed in the transition metal catalyzed AAA was reported in 1978 by Kagan.[6] For the reasons stated above, the enantioselectivity was rather low. Since this initial report, only a handful of examples have been subsequently disclosed with similar poor results.[7] Chiral palladium complexes have been used almost exclusively to effect this transformation.[8,9] While the progress toward achieving transition metal catalyzed AAA using prochiral enolates is impressive, the method is somewhat limited as "soft", stabilized carbanions are typically employed. The extension of this reaction to include simple ketone enolates such as that of cyclohexa-

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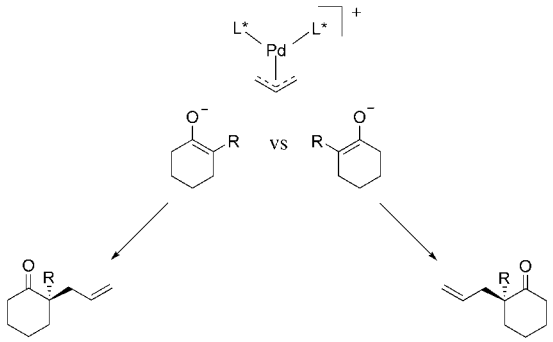
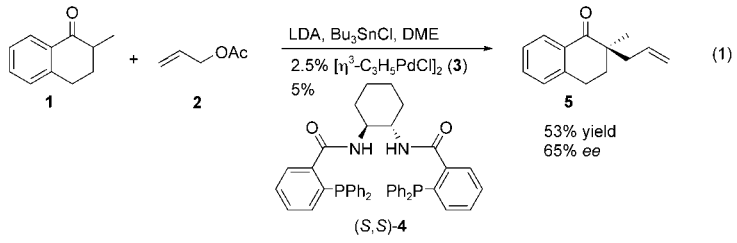


Figure 1. Transition metal catalyzed AAA of prochiral nucleophiles.

none would represent a significant achievement. The compatibility of such hard nucleophiles with palladium in the AAA reaction has since been explored. We recently disclosed in a preliminary communication our efforts toward affecting the palladium-catalyzed AAA of nonstabilized ketone enolates to generate quaternary centers.[10] Herein, we describe in detail its successful application.

Results

Reaction optimization: 2-Methyl-1-tetralone (**1**) was chosen for initial examination as the nucleophile in the presence of allyl acetate (**2**) as the electrophile, LDA as the base, 1,2-dimethoxyethane (DME) as the solvent, and a catalytic amount of a chiral palladium complex formed from π-allyl palladium chloride dimer **3** and cyclohexyldiamine derived chiral ligand **4** [Eq. (1)]. A Lewis acid, tributyltin chloride, was also added with the thought that the Lewis acid would "soften" the lithium enolate by transmetallation to form the tin derivative. Gratifyingly, the reaction was found to proceed to give the desired alkylated product **5** in 53% yield and moderate enantiomeric excess (65% *ee*). Given this initial success the Lewis acid additive, base, solvent, and palladium source were systematically varied.



While the addition of a Lewis acid was thought to help stabilize the very reactive ketone enolate, it also provided an additional variable for altering the enolate structure. Thus, a variety of Lewis acids were examined as additives (Table 1). One trend observed in variation of the Lewis acid was a correlation between Lewis acid size and *ee*. In general, the smaller the Lewis acid, the higher the *ee* obtained in the reaction of tetralone **1** with acetate **2**. For example, trimethyltin chloride gave allylated product **5** in 69% *ee* whereas tributyltin chloride gave **5** in 65% *ee* (entry 1 vs 2). Another interesting trend was observed; the yield and enantioselectivity of the reaction was found to correlate with the leaving group ability of the Lewis acid (entries 1, 3–7). Lewis acids with poor leaving groups gave better results than those with good leaving groups. For example, tributyltin chloride proved superior to the corresponding acetate, triflate, and iodide. The reversal in the sense of enantioselectivity using tributyltin fluoride is a remarkable and curious result (entry 7). Several boranes and borates were also found to be competent; however, stannanes gave superior enantioselectivity than did the boron derived Lewis acids. For example, trimethyltin chloride gave better *ee* (69%) than did trimethylborate (58% *ee*, entry 9). A variety of aluminum, indium, titanium, and cerium enolates were found to be ineffective resulting in either little or no reaction. Given these results, trimethyltin chloride became the Lewis acid of choice.

Table 1. Selected optimization studies in variation of the Lewis acid for Equation (1).[a]

Entry	Lewis acid	Yield **5** [%][b]	*ee* **5** [%][c]
1	Bu_3SnCl	53	65
2	Me_3SnCl	65	69
3	$Bu_2Sn(OAc)_2$	NR	–
4	Bu_3SnOAc	trace	–
5	Bu_3SnOTf	21	32
6	Bu_3SnI	28	35
7	Bu_3SnF	78	–25
8	Bu_2BOTf	NR	–
9	$B(OMe)_3$	65	58

[a] All reactions were performed using 1 equiv LDA, 1.05 equiv Lewis acid, 1.1 equiv allyl acetate (**2**), 2.5% **3**, and 5% **4** at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC.

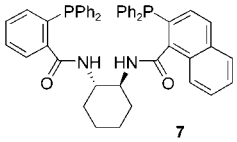
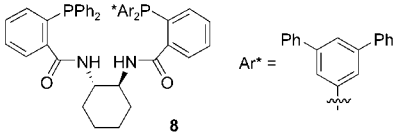
A dramatic effect on the reaction yield was observed in variation of the base (Table 2). Enolates generated from lithium amide bases were found to react readily; whereas, those generated from sodium and potassium bases resulted in recovery of the starting material (entries 1, 2 vs 3). Furthermore, the reaction was found to be sensitive to the amount of base used. For example, on increasing the equivalents of LDA from 1 to 1.25, 1.5, and 2, the enantioselectivity gradually increased (entries 3–7). With three equivalents of LDA, a slight decrease in enantioselectivity was observed, thus two equivalents of base gave the best results and allowed for isolation of allylated tetralone **5** in excellent yield (99%) and *ee* (88%). Importantly, when employing two equivalents of base, the reaction could be run in the absence of the tin additive and gave the allylated product in 96% yield and slightly diminished *ee* (85%, entry 8). Other lithium amide bases (LiHMDS and

Table 2. Variation of the base for Equation (1).[a]

Entry	Base	Equivalents	Additive	Yield **5** [%][b]	*ee* **5** [%][c]
1	KHMDS	1	Me_3SnCl	NR	–
2	NaH	1	Me_3SnCl	NR	–
3	LDA	1	Me_3SnCl	65	69
4	LDA	1.25	Me_3SnCl	78	78
5	LDA	1.5	Me_3SnCl	99	80
6	LDA	2	Me_3SnCl	99	88
7	LDA	3	Me_3SnCl	61	84
8	LDA	2	None	96	85
9	LiHMDS	1	Me_3SnCl	58	61
10	LiHMDS	2	Me_3SnCl	94	71
11	LTMP	1	Me_3SnCl	74	63
12	LTMP	2	Me_3SnCl	99	86

NR = No Reaction. [a] All reactions were performed using 1.1 equiv allyl acetate (**2**), 2.5% **3**, and 5% **4** at room temperature unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC.

Table 3. Variation of the ligand for Equation (1).[a]

Entry	Ligand	Yield **5** [%][b]	*ee* **5** [%][c]
1	**4**	99	88
2	 **7**	81	86
3	 **8**	90	86

[a] All reactions were performed with 1.05 equiv allyl acetate, 1 equiv trimethyltin chloride, 2 equiv LDA, 2.5% **3**, and 5% (*S*,*S*)-ligand in DME at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC.

lithium tetramethylpiperide) also followed this trend with excess base consistently giving higher levels of enantioselectivity (entries 9–12). The amine of the base, a stoichiometric by-product in enolization, affected the enantioselectivity of the reaction as hexamethyldisilazide gave inferior results (entry 10). On the other hand, changing the amide to piperidide had little effect (entry 12).

Variation of the reaction solvent was examined. Moderate enantioselectivity was achieved in all solvents examined including THF, a 10% HMPA/THF solvent mixture, DME, dichloromethane, and toluene. The highest enantiomeric excess and shortest reaction times were achieved in DME, thus it became the solvent of choice.

Two sources of palladium were tried, π-allylpalladium chloride dimer **3** and dibenzylideneacetone complex $[Pd_2dba_3]\cdot CHCl_3$ (**6**). π-Allylpalladium chloride dimer **3** was found to give slightly higher *ee* than dba complex **6**. This may be an indication that the achiral dba competes to some extent with the chiral ligand for palladium. Importantly, use of the opposite enantiomer of the ligand gave the opposite enantiomer as the major product as indicated by chiral HPLC and the sign of the optical rotation. The control experiment in which no palladium was added gave no reaction and indicates minimal or no background reaction.

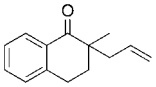
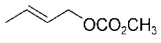
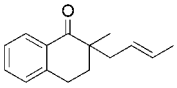
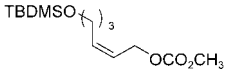
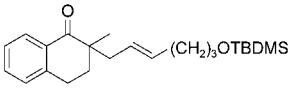
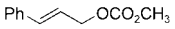
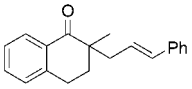
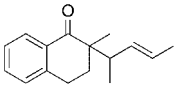
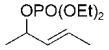
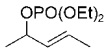
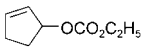
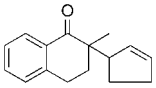
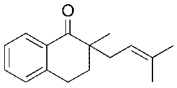
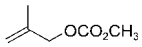
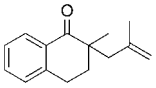
X-ray crystal structures of a related family of ligands suggest that they are not C_2-symmetric as one might suppose.[11] Two non C_2-symmetric ligands were tried in an attempt to ascertain whether a more pronounced deviation from C_2 symmetry impacted the reaction and could possibly result in enhanced enantioselectivity. As shown in Table 3, all reactions gave similar yields and enantioselectivities. Reactions with naphthyl-phenyl ligand **7** were notably slower than those with the standard ligand **4**. Likewise, reactions using 2-isopropyl-1-tetralone as the nucleophile gave the corresponding allylated product in similar *ee* (35% with **4** and 28% with **7**). Thus non C_2-symmetric ligands did not provide any advantage over standard ligand **4**.

To summarize, optimization showed that the best conditions for alkylation of 2-methyl-1-tetralone (**1**) with allyl acetate (**2**) consisted of running the reaction with two equivalents of LDA as the base, palladium dimer **3**, and chiral ligand **4** in DME as solvent. A slightly higher *ee* in the presence of trimethyltin chloride led us to adopt its addition as part of our standard protocol. Under these conditions, the allylated product **5** was isolated in 99% yield and 88% *ee*.

Reaction scope—Variation of the electrophile: With optimized conditions in hand, a variety of allylating agents was explored (Table 4). Crotyl methyl carbonate gave the alkylated product **9** in good yield (84%) and outstanding *ee* (90%) (entry 2). Linearly substituted allyl systems starting from either *E* or *Z* isomers gave products of only *E* geometry in good *ee* (entry 3). Thus, π–σ–π equilibration was faster than nucleophilic attack. Unfortunately, cinnamyl methyl carbonate gave very poor conversion (entry 4). The poor conversion likely results from the formation of a more stable and therefore less reactive palladium π-allyl complex. A 1,3-dialkyl allylic carbonate, gave the alkylated product **12** in excellent *ee* and *de*, but in disappointing yield (17%). The yield could be improved on switching to the more reactive allylic phosphate and increasing the amount of electrophile added (entry 7). At the end of the reaction, no electrophile remained by TLC. Presumably, the yield of this reaction could be further improved by adding additional electrophile or by increasing the concentration of the reaction. The ability to control the stereoselectivity at the nucleophile as well as at the electrophile is remarkable. A cyclic analogue gave the alkylated product **13** in good yield, but poor *ee* (entry 8). A 1,1-dialkyl system and a branched allyl system gave disappointing results (entries 9–10). To summarize, linearly substituted, acyclic 1,3-dialkyl substituted, and unsubstituted π-allyls (allyl acetate) gave the best results.

Reaction scope—Variation of the nucleophile: A variety of α-tetralone derived nucleophiles were examined in the palladium-catalyzed AAA with allyl acetate (**2**) (Table 5).[12,13] Substitution in the 2-position of α-tetralone was tolerated when the substituent was not too sterically demanding. The methyl, ethyl, benzyl, and allyl groups all gave comparable

Table 4. Reaction scope: Variation of the electrophile.[a]

Entry	Electrophile	Product	Yield [%][b]	*ee* [%] (*de*)[c]
1	allyl acetate (**2**)	 **5**	99	88
2		 **9**	84	90
3		 **10**	72	82
4		 **11**	11	–
5		 **12**	16	>95 (91)
6		**12**	17	>95 (>95)
7[d]		**12**	41	>95 (>95)
8[e]		 **13**	87	37
9		 **14**	64	13
10		 **15**	82	47

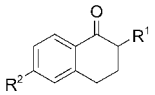
[a] All reactions were performed with 1.05–1.1 equiv electrophile, 1 equiv trimethyltin chloride, 2 equiv LDA, 2.5% **3**, and 5% (*S*,*S*)-**4** in DME at room temperature unless otherwise indicated. [b] Isolated yield. [c] Determined by chiral HPLC or chiral GC. [d] Two equivalents of electrophile were used. [e] The enantioselectivity at the nucleophile was determined after hydrogenation of the olefin.

results with *ee* values varying from 73–88% (entries 1, 2, 4, 5). In the case of allyl substituted α-tetralone, crotyl methyl carbonate was used as the electrophile (entry 5). Unfortunately, a more bulky isopropyl group gave significantly diminished *ee* (35%, entry 3). A methoxy substituted tetralone also gave good yield (83%) and *ee* (85%) (entry 6).

The ring size of the nucleophile was varied and the five- and seven-membered ring analogues were examined (Scheme 1). Commercially available 2-methyl-1-indanone gave the allylated product **21** in a disappointing 38% *ee* (79% yield) with allyl acetate as the electrophile. Likewise methyl substituted benzosuberone[13] gave ketone **22** in only 6% *ee*. Thus, these reaction conditions appear to be limited to six-membered ring cycloalkanones. A furan analogue of tetralone **1** was also tried, unfortunately, application of the standard reaction conditions to this substrate gave modest *ee* (45%).[14]

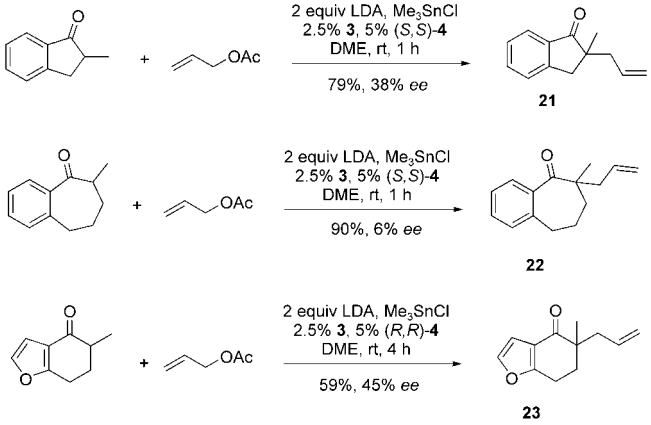
The palladium-catalyzed AAA was applied to some α′-blocked, α-alkyl cyclohexanones. Benzylidene,[15] furanylidene,[16] and ketene dithioacetal[17] substituted cyclohexanones were examined in their reaction with allyl acetate (Scheme 2). The benzylidene cyclohexanone gave allylated product **24**[18] in nearly quantitative yield (98%) and 82% *ee* at room temperature. In the case of the furanylidene derivative, a temperature effect was explored. At room temperature, the product **25** was produced in only 79% *ee* (89% yield), whereas at 0°C the enantiomeric excess increased to 92% (95% yield). A similar effect was observed with the ketene dithioacetal substituted cyclohexanone. In this case the reaction at room temperature gave ketone **26** of 70% *ee* (64% yield). At 0°C, an improved 79% *ee* (51% yield) was obtained. Finally, at −10°C the allylated product was isolated in 67% yield and 82% *ee*. Two equivalents of allyl acetate were used in the experiment at −10°C to help maintain the rate of reaction.

Table 5. Reaction scope: Variation of the nucleophile.[a]

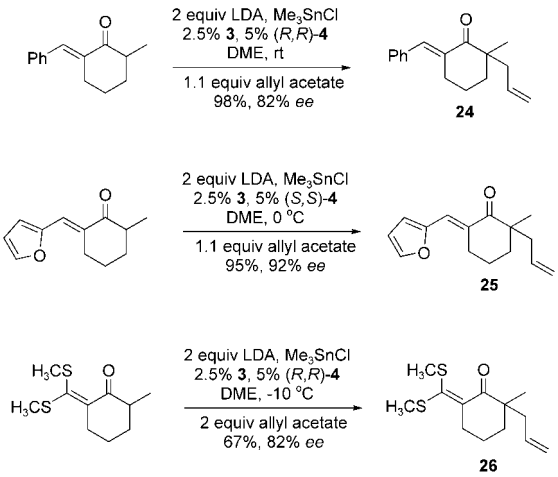


Entry	R^1	R^2	Product, yield [%][b]	*ee* [%][c]
1[d]	CH_3	H	**5**, 99	88
2	C_2H_5	H	**16**, 96	80
3	$CH(CH_3)_2$	H	**17**, 99	35
4	CH_2Ph	H	**18**, 98	73
5[e]	$CH_2CH=CH_2$	H	**19**, 71	85
6	CH_3	OCH_3	**20**, 83	85

[A] All reactions were performed with 1.1 equiv allyl acetate, 1 equiv trimethyltin chloride, 2 equiv LDA, 2.5% **3**, and 5% (*R*,*R*)-**4** in DME at room temperature unless otherwise indicated. [b] Isolated yield. [c] Determined by chiral HPLC. [d] (*S*,*S*)-**4** was used. [e] Crotyl methyl carbonate was used as the electrophile.



Scheme 1. Variation of the ring size.

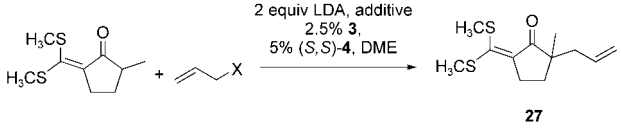


Scheme 2. AAA of cyclohexanones.

Given our success with the six-membered ring ketene dithioacetal and the versatility of the ketene dithioacetal moiety, five membered-ring analogues were tried (Table 6).[16] Application of the standard reaction conditions to a methyl ketene dithioacetal derivative gave the allylated product **27** in low yield (35%) and modest *ee* (52%) (entry 1). Decreasing the reaction temperature did give improved yield (64%) and *ee* (64%, entry 2), however further lowering of the reaction temperature led to poor conversion. Switching to a more reactive electrophile, allyl chloride, allowed the reaction to proceed at −15°C and gave **27** in 70% *ee* (53% yield, entry 3). Once again, further reductions in the reaction temperature failed to give improved results and resulted in recovery of the starting material (entry 4). Performing the reaction in the absence of trimethyltin chloride had a slight negative effect on the *ee* (58%, entry 5).

Due to the modest yield and *ee* in generating ketene dithioacetal **27**, the thioalkyl group was varied. The ethyl derivative was tried next with the thought that increasing the steric bulk of the ketene dithioacetal would allow for more effective facial discrimination of the approaching nucleophile by the chiral ligand [Eq. (2)]. Disappointingly, palladium catalyzed AAA with allyl acetate at 0°C gave the allylated product in poor yield (42%) and *ee* (49%).

Table 6. Synthesis of ketene dithioacetal **27**.[a]

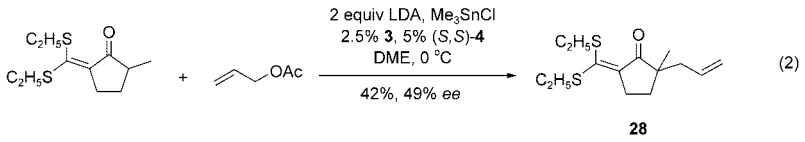


Entry	Additive	T[°C]	X	Yield **27** [%][b]	*ee* **27** [%][c]
1	Me_3SnCl	rt	OAc	35	52
2[d]	Me_3SnCl	0	OAc	64	64
3[d]	Me_3SnCl	−15	Cl	53	70
4[d]	Me_3SnCl	−20	Cl	trace	–
5[d]	None	0	OAc	40	58

[a] All reactions were performed with 1.1 equiv electrophile, 1 equiv additive, 2 equiv LDA, 2.5% **3**, and 5% (*S,S*)-**4** in DME unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Two equivalents of electrophile were used.

A more rigid cyclic ketene dithioacetal was also examined [Eq. (3)]. Reaction under the standard conditions gave the allylated product **29** in good yield (76%) and modest *ee* (57%) at room temperature. The improved yield stems from increased stability of the cyclic ketene dithioacetal to the reaction conditions as noted by the fact that the reactions were noticeably cleaner. Like the previous examples, the *ee* could be increased to 63% by lowering the reaction temperature to 0°C. Unfortunately, further decreases in the reaction temperature gave diminished yield.

Due to the disappointing results with ketene dithioacetals, we turned our attention to enol ether nucleophiles. Reaction of a *tert*-butyl enol ether with allyl acetate under the standard reaction conditions was examined to give allylated product **30** [Eq. (4), Table 7)]. Surprisingly, the enantioselectivity of the reaction varied widely with different bottles of *n*-butyllithium. It was thought that perhaps the difference in behavior was due to the presence of varying amounts of alkoxides in the bottles, thus *tert*-butanol was added to the reaction (entries 1–4). A clear dependence of the enantioselectivity of the reaction on the amount of *tert*-butanol added was observed. A gradual increase in *ee* was observed as the



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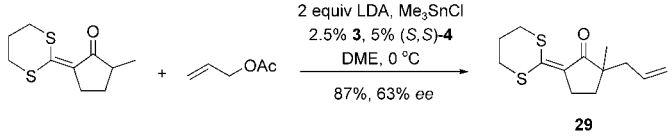


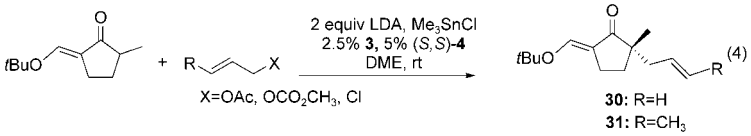
(3)

Table 7. Synthesis of *tert*-butyl enol ether **30**.[a]

Entry	*t*BuOH (equiv)	Yield **30** [%][b]	*ee* **30** [%][c]
1	1	85	15
2	3	86	79
3	5	80	89
4	7	87	91
5[d]	7	83	95

[a] All reactions were performed with 1.1 equiv allyl acetate, 1 equiv trimethyltin chloride, 2 equiv LDA, 2.5% **3**, and 5% (*S*,*S*)-**4** in DME at room temperature unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2.2 Equiv electrophile and 1 mol% catalyst were used.

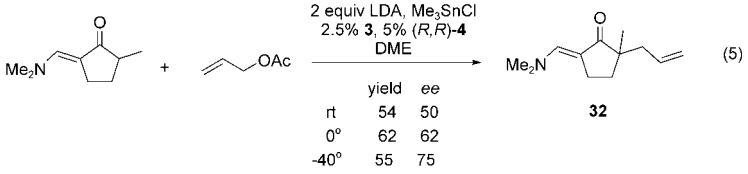
amount of *tert*-butanol added was increased from one to three to five and finally to seven equivalents. The *ee* seemed to plateau at 7 equiv *tert*-butanol, thus these became the conditions of choice and allowed for isolation of **30** reliably in 87% yield and 91% *ee* (entry 4). Gratifyingly, the catalyst loading could be reduced to 1 mol% without significant loss of chemical yield and with an improved 95% *ee* (entry 5). The six-membered ring analogue was also tried in this reaction. Surprisingly, the cyclohexanone derivative was found to give the product in very low *ee* in the presence and absence of *tert*-butanol (5 and 1%, respectively). The reason for this dramatic difference in reaction is not clear.



With optimized conditions in hand, the reaction was tried with crotyl derived electrophiles [Eq. (4), Table 8]. In the presence of crotyl methyl carbonate, the alkylated product **31** was isolated in 71% yield and 81% *ee* (entry 1). The reaction was somewhat slow and required several hours, thus the more reactive crotyl chloride was tried. At 0°C, the reaction gave **31** in 71% yield (84% *ee*, entry 2). The enantiomeric excess increased to 87% when the reaction was performed at −20°C (entry 3). Also, the catalyst loading could be decreased to 2 mol% without affecting the yield or *ee* (entry 4). A crotyl phosphate was also tried as the electrophile and gave the desired product in similar yield and *ee* (entry 5). To conclude, alkylated ketone **31** could be obtained in 70–80% yield and 81–88% *ee* under a variety of conditions.

The AAA reaction of a nitrogen analogue was briefly examined [Eq. (5)].[19] The traditional conditions without *tert*-butanol were tried and a pronounced temperature effect was observed. Thus, on decreasing the reaction temperature from room temperature to 0 to −40°C, the *ee* of product **32** increased from 50 to 62 to 75% without affecting the yield of the reaction (54, 62, and 55%, respectively). No further attempts were made to increase the yield and enantioselectivity of this reaction.

The allylated products generated in this reaction are versatile substrates for further transformations. For example, 1,3-carbonyl transposition[20] of keto ketene dithioacetal **26** gave α,β-unsaturated thiol ester **33**, a useful substrate for annulation protocols[21] [Eq. (6)]. The use of mercuric chloride to effect dehydration of the intermediate alcohol was critical as use of 10% HCl/MeOH or acidic silica gel gave significant amounts of side products resulting from capture of the stable allylic carbocation intermediate by methanethiol.



Likewise, *tert*-butyl enol ether **31** proved a versatile compound for further elaboration (Scheme 3). Treatment of **31** with methyllithium gave aldehyde **34** in 81% yield. The in-

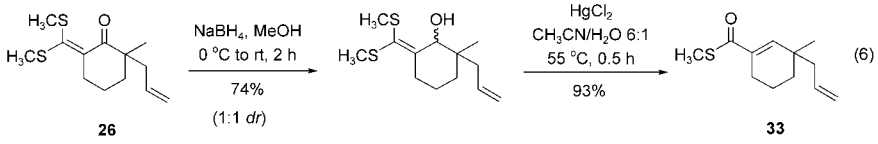
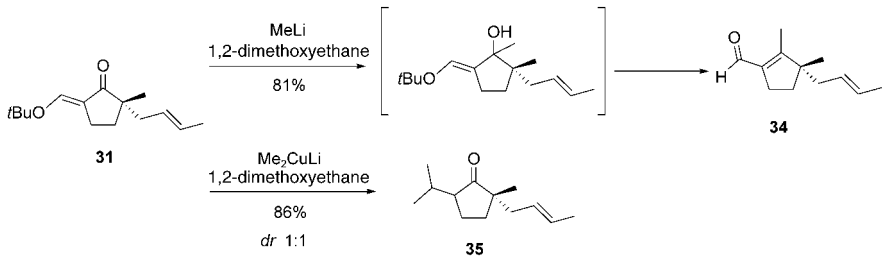


Table 8. Synthesis of *tert*-butyl enol ether **31**.[a]

Entry	Electrophile	(equiv)	*T* [°C]	Yield **31** [%][b]	*ee* **31** [%][c]
1	OCO_2CH_3	(1.1)	rt	71	81
2	crotyl chloride	(2.2)	0	71	84
3	crotyl chloride	(2.2)	−20	61	87
4[d]	crotyl chloride	(2.2)	0	74	84
5	$OPO(OEt)_2$	(2.2)	0	73	82

[a] All reactions were performed with 1 equiv trimethyltin chloride, 2 equiv LDA, 2.5% **3**, and 5% (*S*,*S*)-**4** in DME unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Two mol% catalyst was used.

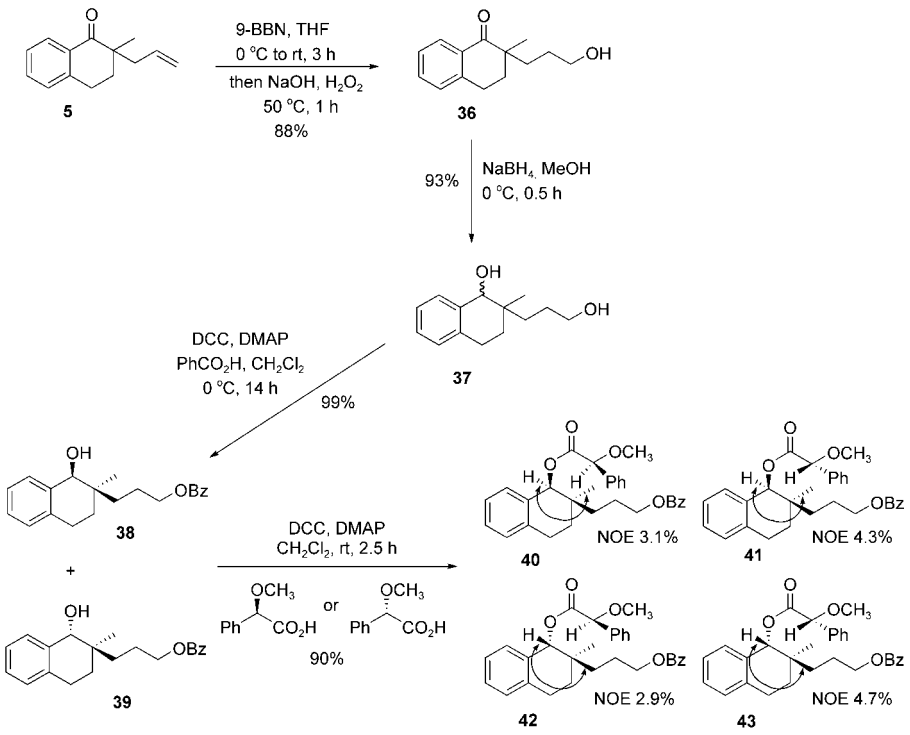


Scheme 3. Versatility of enol ether **31**.

termediate alcohol was never isolated as it eliminated *tert*-butanol upon work-up. Remarkably, this reaction accomplished a 1,3-carbonyl transposition while forming a new carbon–carbon bond in a single step. On the other hand, treatment of enol ether **31** with two equivalents of lithium dimethylcuprate gave ketone **35** in 86% yield as a 1:1 mixture of diastereomers. Thus, addition of one equivalent of lithium dimethylcuprate was followed by elimination of *tert*-butanol and addition of a second equivalent of lithium dimethylcuprate to give the desired product. The intermediate enone was never observed as the second addition was much more facile than the first.

To conclude, a variety of α-tetralone, cyclohexanone, and cyclopentanone nucleophiles can be employed in the palladium-catalyzed AAA with a range of electrophiles to give the corresponding alkylated products in good yield and *ee*. For cyclohexanones, the benzylidene, furanylidene, or ketene dithioacetal groups are compatible with the reaction. For cyclopentanones, a *tert*-butyl enol ether gave excellent results.

Determination of the absolute stereochemistry: The absolute configuration of allylated tetralone **5** was determined as shown in Scheme 4. The terminal olefin of **5** was hydroborated and oxidized to give the corresponding primary alcohol **36** in 88% yield.[22] Reduction of the ketone with sodium borohydride gave a diasteromeric mixture of diols **37**. Chemoselective protection of the primary alcohol as the benzoate allowed for separation of the two diastereomers by column chromatography. Each diastereomer was then reacted with (*S*)- and (*R*)-(*O*-methoxy)mandelic acid to give enantiomerically pure mandelate esters **40**–**43**. To determine the relative configuration between the benzylic alcohol and the adjacent quaternary center, NOE studies were performed. Strong NOE values (2.9–4.7%) were observed between the benzylic hydrogen and the methyl group or alkyl benzoate. With knowledge of the relative stereochemistry in hand, the characteristic shielding effect of the mandelate phenyl group allowed for determination of the absolute stereochemistry as shown in Figure 2.[23]

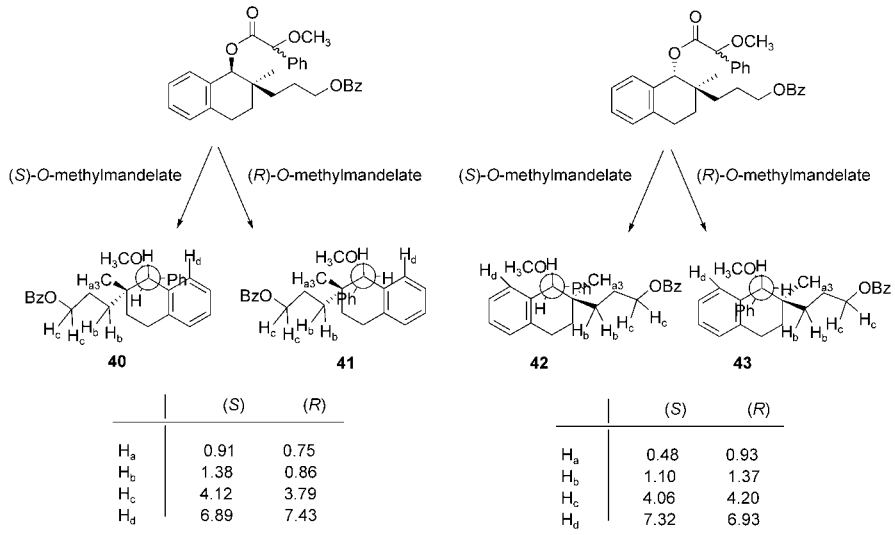


Scheme 4. Assignment of the absolute configuration.

In the ^{1}H NMR spectra of ester **40**, the signal for the aromatic proton (H_d) was shifted to higher field than the corresponding proton in ester **41**. As illustrated in the Newman projection of **40**, H_d is shielded by the *O*-methylmandelate ester's phenyl ring only if the absolute stereochemistry of the quaternary center is (*R*). By analogy, in the ^{1}H NMR spectra of ester **41** the signals for the methyl group (H_a) as well as H_b and H_c were shifted to higher field than the corresponding protons in ester **40**. Again, the Newman projection **41** illustrates the shielding by the *O*-methylmandelate ester's phenyl ring which can only occur if the quaternary center is (*R*).

Discussion

In palladium-catalyzed AAA of prochiral nucleophiles, the structure of the nucleophile plays a critical role in discrimi-



	40 (S)	40 (R)	41 (S)	41 (R)
H_a	0.91	0.75	0.48	0.93
H_b	1.38	0.86	1.10	1.37
H_c	4.12	3.79	4.06	4.20
H_d	6.89	7.43	7.32	6.93

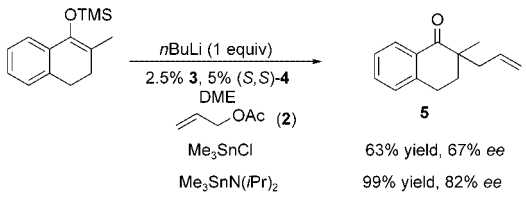
Figure 2. Extended Newman projections of mandalate esters **40**–**43**.

nation of the enantiotopic facial approaches by the chiral catalyst. The importance of enolate structure is evidenced by the strong dependence of reactivity and enantioselectivity on the choice of base, Lewis acid additive, and solvent. Choice of base proved critical as only lithium enolates were competent in the reaction. One possible explanation for this observed reactivity is that the more oxaphilic lithium atom is better able to stabilize the very reactive ketone enolate. The harder sodium and potassium enolates may react with the palladium catalyst rendering it catalytically inactive. As an alternative explanation, the effect of lithium might result from the difference in size of the enolate counterions with lithium being the smallest and therefore least sterically demanding counterion, allowing the nucleophile to access the chiral pocket created by the palladium and ligand. One unknown issue is the effect of aggregation of the various enolates on both reactivity and enantioselectivity.

Several explanations for the dependence of the *ee* on the amount of base can be proposed: one, the excess base could deprotonate the ligand, thereby altering the nature of the chiral environment; two, the excess base could form an aggregate with the nucleophile, changing the nature of the nucleophile; three, the excess base could hydrogen bond with the amine by-product generated during enolization, thereby preventing the amine from associating with the nucleophile; last, the excess base could react with the Lewis acid additive, trimethyltin chloride, forming the corresponding amino stannane.

To explore the hypothesis that excess LDA was exerting its beneficial effect by deprotonation of the amide hydrogens of the ligand, the ligand was intentionally deprotonated prior to addition to the reaction mixture. The palladium catalyst, prepared from palladium dimer **3** and ligand **4**, was deprotonated with trityllithium to presumably generate the dianion of the ligand and then the dianion was used in the usual manner in the AAA, but using just one equivalent of base to generate the enolate. Contrary to this hypothesis, the allylated product was obtained in only 70% yield and 67% *ee*.

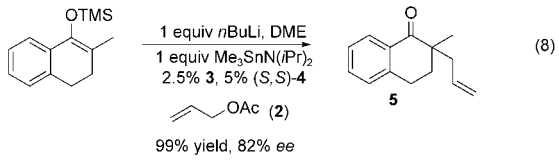
To address the possibility that the amine by-product from the lithium amide base was affecting the reaction, the silyl enol ether of 2-methyl-1-tetralone (**1**) was prepared and treated with allyl acetate [Eq. (7)]. Alkylation was achieved by cleaving the silyl enol ether with *n*BuLi, generating a reaction mixture which was free from the stoichiometric amine by-product. The enantiomeric excess of this reaction was determined to be much lower (67%) than that in the presence of the amine by-product (88%). This experiment clearly indicates a role for the amine in the reaction. Further evidence for this assumption can be found in Table 2 which demonstrates a dependence of enantioselectivity on the choice of lithium amide base with LDA and LTMP giving higher *ee* than LiHMDS.



(7)

To investigate the possibility that the aminostannane is formed from trimethyltin chloride and excess LDA, (diisopropylamino)trimethyltin was independently synthesized[24] and tried in the AAA of the silyl enol ether of **1** [Eq. (8)]. After cleaving the silyl enol ether with one equivalent of *n*BuLi and treating the resulting lithium enolate with one equivalent of the aminostannane, the allylated product **5** was isolated in quantitative yield and 82% *ee*. Since it was shown that the analogous reaction using trimethyltin chloride generated the product in just 63% yield and 67% *ee* [Eq. (7)], these results support the idea that the amino stannane is formed and may be responsible at least in part for the enhanced enantioselectivity when two equivalents of base are employed. Presumably, the only difference between the reaction conditions in Equation (8) and the standard conditions is the presence of lithium chloride. The reaction depicted in Equation (8) was performed in the presence of one equivalent of lithium chloride to see if the *ee* would rise to 88%. Tetralone **5** was isolated in quantitative yield and 83% *ee*, therefore the addition of lithium chloride failed to further enhance the enantioselectivity. It should be noted

that the low solubility of lithium chloride in DME complicates the interpretation of this result.



(8)

Given the dependence of enantioselectivity on the amine portion of the base and the hypothesis that an aminostannane is formed in the reaction, one would expect a dependence of *ee* on the amine portion of the aminostannane. This was indeed found to be the case. Replacement of one of the isopropyl groups with *tert*-butyl gave the allylated product in similar yield and *ee*. However, when the reaction was run in the presence of (dimethylamino)trimethyltin the yield and *ee* dropped to 48 and 73%, respectively. Also, replacement of the amine group by methoxy resulted in lower *ee* (75%, 60% yield).

An alternative explanation for the role of the Lewis acid additive could be that an ate complex rather than a simple trialkylstannyl ether may more accurately describe the nucleophile (Figure 3). The reactivity and enantioselectivity correlated with the leaving group ability on the tin (Table 1). Lewis acids with poor leaving groups gave better results than those with good leaving groups. The amine by-product could then be exerting its effect on this species by displacement of the chloride or by affecting the state of aggregation.

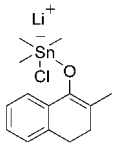


Figure 3. Tin–Ate complex.

Further evidence for the importance of the state of aggregation comes from the dependence of the enantioselectivity on the choice of solvent. The *ee* increased on going from toluene to THF and then to DME. The ability of solvent to affect the state of aggregation of the enolate may be the source of this selectivity. Of the solvents examined, DME is the solvent most capable of breaking up aggregates. The lithium enolate of α-tetralone has been shown to be predominately a monomer–tetramer equilibrium in THF, but with the addition of a 2-isopropyl group the enolate is predominately a dimer.[25] Studies of 2-phenyl-1-tetralone show that the lithium enolate exists as a monomer–dimer mixture and that the equilibrium lies in favor of the dimer (>90%) at concentrations usually used in synthesis (>0.1 M).[26] However, in the case of 2-phenyl-1-tetralone, the dimer was shown to be much less reactive in alkylation reactions than the monomer. Clearly, the exact nature of the nucleophile is a complicated picture with a pronounced effect on this reaction.

Linearly substituted, 1,3-disubstituted, and unsubstituted (allyl acetate) electrophiles functioned well, however, substitution in the two position of the π-allyl was not tolerated. The poor enantioselectivity obtained with a 2-methallyl electrophile may lie in the fact that the π-allyl is canted such that the substituent in the 2-position is pointed toward the ligand and results in an unfavorable steric interaction. The poor results obtained with a cyclic electrophile can also be explained in terms of the structure of the π-allyl palladium complex. Acyclic electrophiles can form a variety of palladium π-allyl complexes with the *syn–syn* form being the lowest energy (Figure 4). Cyclic electrophiles can only exist in the *anti–anti* conformation thus the approaching nucleophile likely encounters a very different environment.

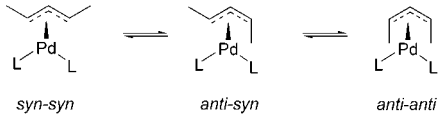


Figure 4. Palladium π-allyl complexes.

The absolute configuration generated from (*S,S*)-**4** is consistent with the current model (Figure 5). In this model, the wall above palladium represents the cyclohexane ring of the ligand and the flaps on either side of palladium represent the phenyl groups on phosphorus. The (*S,S*)-chiral ligand generates (*R*)-allylated product **5** in the allylation of 2-methyl-1-tetralone (**1**). As illustrated by the model, the facial approach leading to (*R*)-**5** allows the nucleophile to approach the π-allyl palladium complex in the open space created by a raised flap. In the alternative approach, the nucleophile encounters unfavorable steric interactions with one of the flaps or phenyl groups of the chiral ligand. Thus, the trajectory of approach for the (*R*)-product is less sterically hindered than the approach which generates (*S*)-**5**. The dependence of the enantioselectivity of the reaction on the substituent in the 2-position of α-tetralone can be rationalized with this model. The decrease in *ee* with larger substituents results as the substituent is positioned such that it may interfere with the lowered flap in the trajectory that gives the (*R*)-product. The alternative facial approach allows for the large substituent to be directed toward the open space created by the raised flap and places the aryl portion of the tetralone towards to lowered flap. This competition between the large substituent and the aryl portion of tetralone for the open space results in the lowered enantioselectivity.

While the cartoon in Figure 5 depicts a C_2-symmetrical complex, X-ray crystal structures suggest that this may not be a true representation of the catalyst. The unsymmetrical nature of the chiral complex may lead to a memory effect where its equilibration is required for good enantioselectivity. Thus, fast reactions can lead to low enantioselectivity and slowing the reaction, for example by lowering the reaction temperature, can result in increased *ee*.

Conclusion

The alkylation of simple ketone enolates of cycloalkanones can now by achieved asymmetrically in a catalytic fashion. The optimum conditions consist of performing the reaction

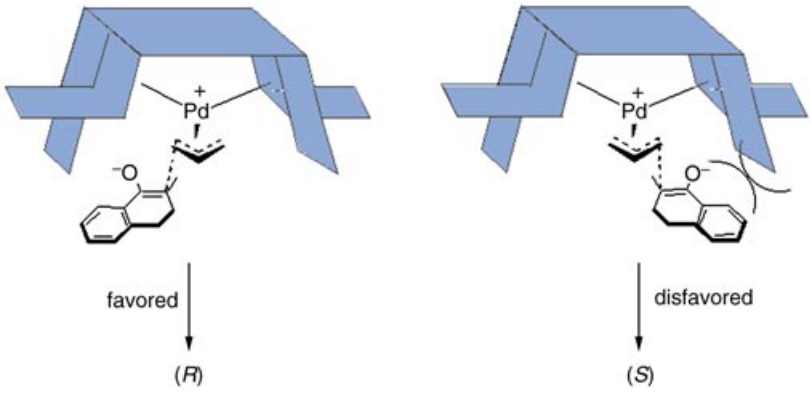


Figure 5. Rationale for chiral recognition.

with two equivalents of LDA and one equivalent of trimethyltin chloride in the presence of chiral ligand **4** using DME as the solvent. Quaternary centers are being formed with a high degree of absolute stereochemical control. The allylated products available by this method are quite versatile for further elaboration.

The importance of the cations associated with the enolate is illustrated by their effect on both reactivity and enantioselectivity. This strongly suggests that the actual structure of the nucleophile is not simple and is likely an aggregate. In employing lithium amide bases such as LDA and LHMDS, there is the possibility of forming LDA-lithium enolate mixed aggregates.[27] As the optimum conditions for AAA call for two equivalents of LDA, one should be especially cognizant of this here. Such aggregates have been crystallized and can themselves form dimers and trimers.[28] Furthermore, the addition of trimethyltin chloride and the production of lithium salts during the reaction of a lithium enolate with an allylic carbonate may cause the nucleophile to possess a variety of structural states during the course of the reaction.

The compatibility of the types of ligands employed, which contain secondary amides, to such strong bases raises questions about whether the amides are deprotonated under the reaction conditions. The success of less stabilized nucleophiles such as simple enolates provides impetus for exploring a much broader range of nucleophiles.

Experimental Section

All palladium reactions were performed under an atmosphere of dry nitrogen in flame-dried glassware. Solvents were distilled under an atmosphere of nitrogen before use and transferred via an oven-dried syringe. *n*BuLi was titrated prior to the preparation of LDA.[29]

Palladium-catalyzed AAA—General procedure A: *n*BuLi (2 equiv) was added at −78 °C to a solution of freshly distilled diisopropylamine (2 equiv) in DME. After stirring at −78 °C for 15 min, a solution of the nucleophile (1 equiv) in DME was added. After stirring at 0 °C for 15 min, a solution of trimethyltin chloride (1 equiv) in DME was added. The enolate solution was stirred at 0 °C for 15 min, cooled to −78 °C, and charged with a prestirred solution (rt, 5 min) of electrophile (1.05–1.1 equiv), palladium dimer **3** (2.5 %), and ligand **4** (5 %) in DME. After the final addition, the concentration of the reaction in nucleophile was 0.18 M. The cooling bath was removed and the reaction was allowed to stir at room temperature until the reaction was complete. The product was purified directly by flash chromatography on silica gel.

A typical example is given as follows: *n*BuLi (370 μL, 0.594 mmol) was added at −78 °C to a solution of freshly distilled diisopropylamine (83 μL, 0.594 mmol) in DME (0.4 mL). After stirring at −78 °C for 15 min, a solution of 2-methyl-1-tetralone (**1**) (48 mg, 0.297 mmol) in DME (0.4 mL) was added. After stirring at 0 °C for 15 min, a solution of trimethyltin chloride (59 mg, 0.297 mmol) in DME (0.4 mL) was added. The enolate solution was stirred at 0 °C for 15 min, cooled to −78 °C, and charged with a prestirred solution (rt, 5 min) of allyl acetate (**2**) (35 μL, 0.327 mmol), palladium dimer **3** (2.7 mg, 0.00742 mmol), and ligand **4** (10.2 mg, 0.0149 mmol) in DME (0.6 mL). The cooling bath was removed and the reaction was allowed to stir at room temperature for 30 min. The product was purified directly by flash chromatography on silica gel eluting with 5 % ethyl acetate/petroleum ether to give tetralone **5** (59 mg, 99 %).

2-Allyl-2-methyl-1-tetralone (5): Prepared using (*S*,*S*)-ligand **4**; $R_f = 0.53$ (10 % ethyl acetate/petroleum ether); determination of enantiomeric excess: HPLC (Chiralcel OD column, 99.9:0.1 heptane/isopropanol, flow = 0.70 mL min^{-1}), t_R (major) enantiomer = 19.14 min, t_R (minor) enantiomer = 17.95 min; $[\alpha]_D = +13.9°$ (c = 1.18, 23.8 °C, dichloromethane, 88 % *ee*); IR (thin film): $\tilde{\nu}$ = 3074, 2930, 1682, 1602, 1455, 1221, 916, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.02 (d, J = 6.9 Hz, 1H), 7.44 (dt, J = 7.5, 1.2 Hz, 1H), 7.31–7.19 (m, 2H), 5.81–5.70 (m, 1H), 5.08–5.03 (m, 2H), 2.96 (t, J = 6.0 Hz, 2H), 2.45 (dd, J = 13.8, 7.2 Hz, 1H), 2.26 (dd, J = 13.8, 7.5 Hz, 1H), 2.15–2.02 (m, 1H), 1.97–1.84 (m, 1H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 202.3, 143.4, 134.1, 133.2, 128.8, 128.1, 126.7, 118.3, 44.6, 41.1, 33.3, 25.3, 21.8; HRMS: m/z: calcd for $C_{14}H_{16}O$: 200.1202; found: 200.1197.

Palladium-catalyzed AAA—General procedure B: *n*BuLi (2 equiv) was added at −78 °C to a solution of freshly distilled diisopropylamine (2 equiv) in DME. After stirring at −78 °C for 15 min, a solution of the nucleophile (1 equiv) in DME was added. After stirring at 0 °C for 15 min, the enolate solution was charged with *t*BuOH (7 equiv) followed by a solution of trimethyltin chloride (1 equiv) in DME. The enolate solution was stirred at 0 °C for 5 min, cooled to −78 °C, and charged with a prestirred solution (rt, 5 min) of electrophile (1.05–1.1 equiv), palladium dimer **3** (2.5 %), and ligand **4** (5 %) in DME. After the final addition, the concentration of the reaction in nucleophile was 0.18 M. The cooling bath was removed and the reaction was allowed to stir at room temperature until the reaction was complete. The product was purified directly by flash chromatography on silica gel.

A typical example is given as follows: *n*BuLi (200 μL, 0.312 mmol) was added at −78 °C to a solution of freshly distilled diisopropylamine (44 μL, 0.312 mmol) in DME (0.2 mL). After stirring at −78 °C for 15 min, a solution of 2-*tert*-butoxymethylene-5-methylcyclopentanone (28 mg, 0.156 mmol) in DME (0.2 mL) was added. After stirring at 0 °C for 15 min, *t*BuOH (100 μL, 1.05 mmol) was added followed by a solution of trimethyltin chloride (31 mg, 0.156 mmol) in DME (0.2 mL) was added. The enolate solution was stirred at 0 °C for 5 min, cooled to −78 °C, and charged with a prestirred solution (rt, 5 min) of allyl acetate (**2**) (19 μL, 0.172 mmol), palladium dimer **3** (1.4 mg, 0.0039 mmol), and ligand **4** (5.4 mg, 0.0078 mmol) in DME (0.3 mL). The cooling bath was removed and the reaction was allowed to stir at room temperature for 1 h. The product was purified directly by flash chromatography on silica gel eluting with 10 % ethyl acetate/petroleum ether to give ether **30** (30.2 mg, 87 %).

2-*tert*-Butoxymethylene-5-methyl-5-(2-propenyl)cyclopentanone (30): Prepared using (*S*,*S*)-ligand **4**. $R_f = 0.48$ (20 % ethyl acetate/petroleum

ether). Determination of enantiomeric excess: chiral GC (cyclosil B, isotherm 120 °C) t_R(major) = 74.825 min, t_R(minor) = 74.169 min; $[\alpha]_D$ = +38.3° (c = 1.37, 23.7 °C, dichloromethane, 96 % *ee*); IR (thin film): $\tilde{\nu}$ = 2977, 2869, 1708, 1630, 1458, 1371, 1265, 1156, 980, 945 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.50 (t, J = 2.5 Hz, 1H), 5.76–5.68 (m, 1H), 5.02 (d, J = 14 Hz, 2H), 2.44–2.41 (m, 2H), 2.15–2.13 (m, 2H), 1.87–1.81 (m, 1H), 1.60–1.55 (m, 1H), 1.34 (s, 9H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 210.9, 149.0, 134.6, 117.6, 115.2, 79.8, 49.5, 41.3, 32.5, 28.3, 22.0, 21.3; elemental analysis calcd (%) for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.84, H 10.18.

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[29] The use of commercially available LDA is not recommended.

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