CHAPTER ONE

Enantioselective Alkylations Generating All-Carbon Quaternary Stereocenters Within Rings

1.1 Background

The catalytic enantioselective preparation of all-carbon quaternary stereocenters has proven challenging for the synthetic chemist.[1] Many elegant methods have been demonstrated, including Diels-Alder reactions,[2] cyclopropanations,[3] desymmetrizations,[4] Heck reactions,[5] acylations,[6] electrocyclizations,[7] arylations,[8] and transformations catalyzed by organic molecules.[9] Another significant approach is the alkylation of prochiral enolates to generate all-carbon quaternary stereocenters.[10,11] Of particular interest are those alkylative methods where the newly formed stereocenter is within a ring because this motif is found in numerous natural products and biologically important pharmaceuticals.

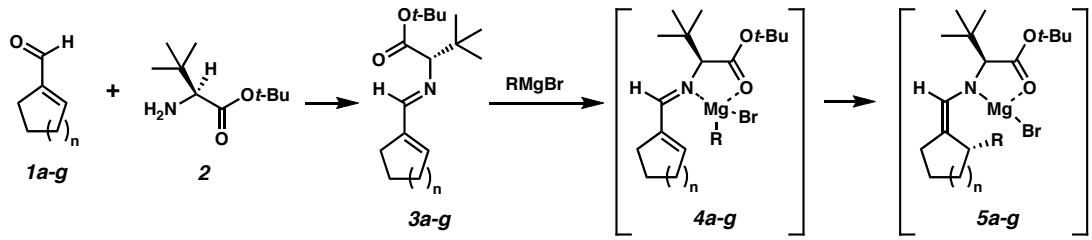
1.2 Auxilliary-Based Methods for Alkylation

1.2.1 *Koga's t-Butyl Glycine Esters*

Koga demonstrated one of the first auxiliary-based methods for setting all-carbon quaternary stereocenters within rings via alkylation.[12] Cycloalkene carbaldehydes (e.g., **1a-g**) were condensed with a *t*-butyl glycine ester (**2**) (Scheme 1.1). Diastereoselective conjugate addition of a Grignard reagent to **3a-g** generated metalloenamines **5a-g**, which were alkylated with iodomethane and hydrolyzed furnishing **6Aa-g**. Alternatively, the auxilliary could be removed after the 1,4-Grignard addition and the resulting aldehydes **7a-g** alkylated with iodomethane, giving diastereomers **6Ba-g**. Both alkylation processes

were highly diastereoselective, and the α-quaternary aldehydes could be accessed in high ee. The auxiliary could also be recycled after completion of the sequences.

Scheme 1.1 Koga's Alkylation of Cycloalkene Carbaldehydes

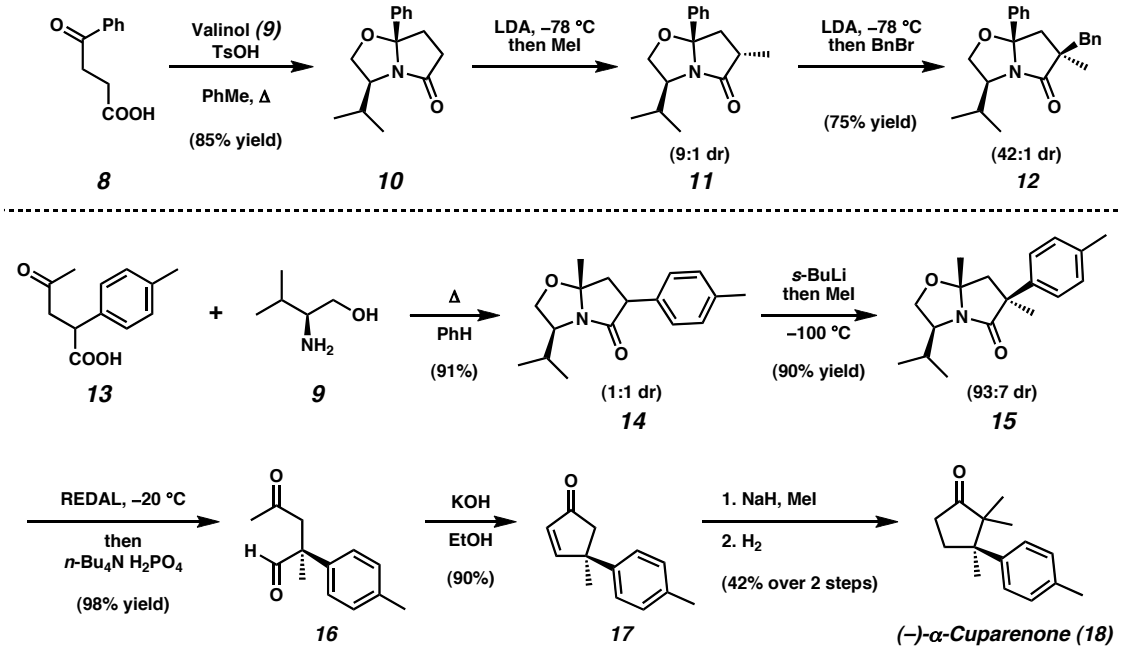


Entry	Method	n	R	% Yield 6Aa-g	% Yield 6Ba-g
a	A	1	Vinyl	62	0
b	A	2	Ph	55	0
c	A	2	Vinyl	67	0
d	B	1	Ph	0	65
e	B	1	Vinyl	0	61
f	B	2	Ph	1	62
g	B	2	Vinyl	11	51

1.2.2 *Meyers' Valinol Auxilliary*

Meyers condensed various γ-keto acids (e.g., **8**) with valinol (**9**) to prepare chiral bicyclic lactams (e.g., **10**, Scheme 1.2).[13] A series of two alkylations were performed, leading to α-quaternary lactams (e.g., **12**) with high diastereoselectivity. Although the first alkylation usually occurred with 9:1 dr or greater, enantioenriched monoalkylated product was usually not obtained presumably due to epimerization during lactam hydrolysis. However, quaternary dialkylated compounds such as **12** were not epimerizable. Hence, the auxiliary could be cleaved under a variety of conditions and the linear product elaborated to a variety of enantioenriched all-carbon quaternary compounds.

Scheme 1.2 Meyers' Valinol Auxilliary Method and Synthesis of Cuparenone



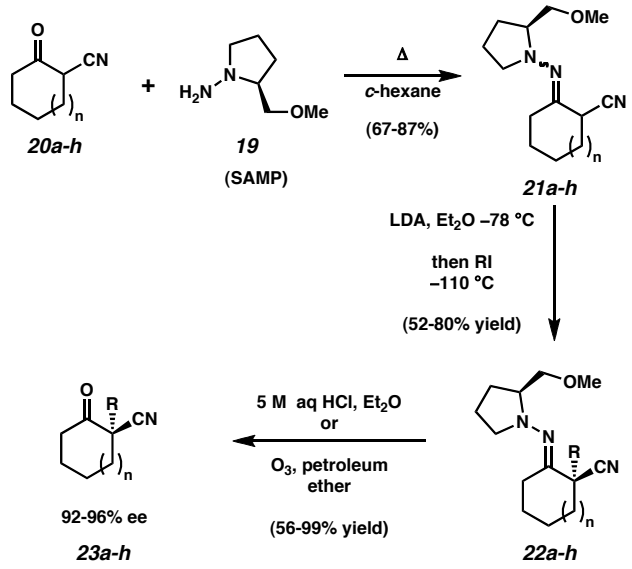
Treatment of pure, crystalline dialkylated lactam **15** with REDAL led to γ-keto aldehyde **16** in 91% yield (Scheme 1.2). Cyclization of **16** under aldol condensation conditions furnished cyclopentenone **17**, which was then alkylated twice with iodomethane. The product was reduced, providing (–)-α-cuparenone (**18**) in 98% ee.[14] This amino alcohol methodology was also used toward the syntheses of other natural products including (+)-mesembrine,[15] (–)-grandisol,[16] and (+)-aspidospermine.[17]

1.2.3 *Enders' RAMP and SAMP Hydrazone Auxilliary*

Enders demonstrated that cyclic ketones themselves could be used as the prochiral enolate precursor. By condensing chiral hydrazine auxilliaries such as (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP) or (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) (**19**) onto β-cyanoketones (e.g., **20a-h**), hydrazones **21a-h** were generated

(Scheme 1.3).[18] Metalloenamine formation was achieved by treating the hydrazones with LDA. Diastereoselective alkylation at low temperature furnished alpha quaternary hydrazones **22a-h** that were readily cleaved (either via acidic hydrolysis or ozonolysis) to afford enantioenriched ketones **23a-h**. This diastereoselective alkylation chemistry is amenable to the preparation of enantioenriched cyclohexanones and cyclooctanones, but 7-membered ring substrates suffer from lower levels of enantioselectivity. Brunner, Kraus, and Lautenschlager described a conceptually similar diastereoselective Michael reaction mediated by an α-methylbenzylamine auxilliary.[11]

Scheme 1.3 RAMP and SAMP Technology



Data for the Alkylation Step
21 → 22

Entry	n	R	% Yield	% de
a	1	Me	68	92
b	1	Et	80	95
c	1	Pr	59	96
d	1	Bu	59	95
e	1	*n*-Hex	73	93
f	2	*	–	77
g	3	Et	66	94
h	3	Pr	49	94

* Alkylating agent was not specified

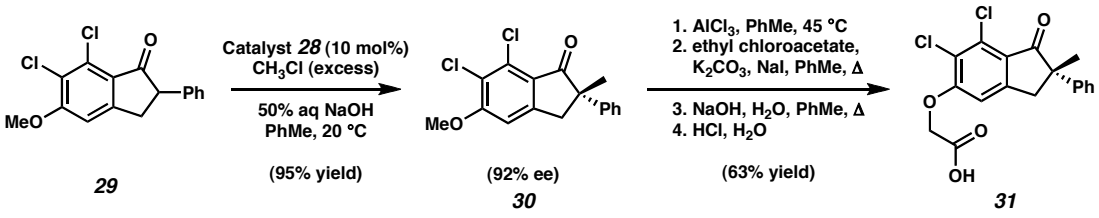
1.3 Catalytic Alkylations for Generating Quaternary Stereocenters without Pd

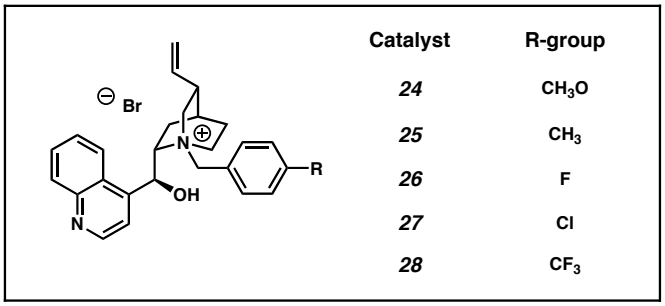
1.3.1 *Chiral Phase Transfer Catalysis*

Catalytic methods for generating all-carbon quaternary stereocenters via alkylation were an attractive alternative to the use of auxiliaries. One of the first

examples employed a chiral phase transfer catalyst, **28**, derived from a cinchona alkaloid (Scheme 1.4).[19] When a biphasic solution of indanone **29** was treated with chloromethane and catalytic **28**, aryl methyl ketone **30** was obtained in 95% yield and 92% ee. This molecule was later advanced to the uricosuric (+)-indacrinone (MK-0197) **31** via a sequence of demethylation and phenolic oxygen alkylation.

Scheme 1.4 Phase Transfer Catalysis for Stereoselective Alkylation





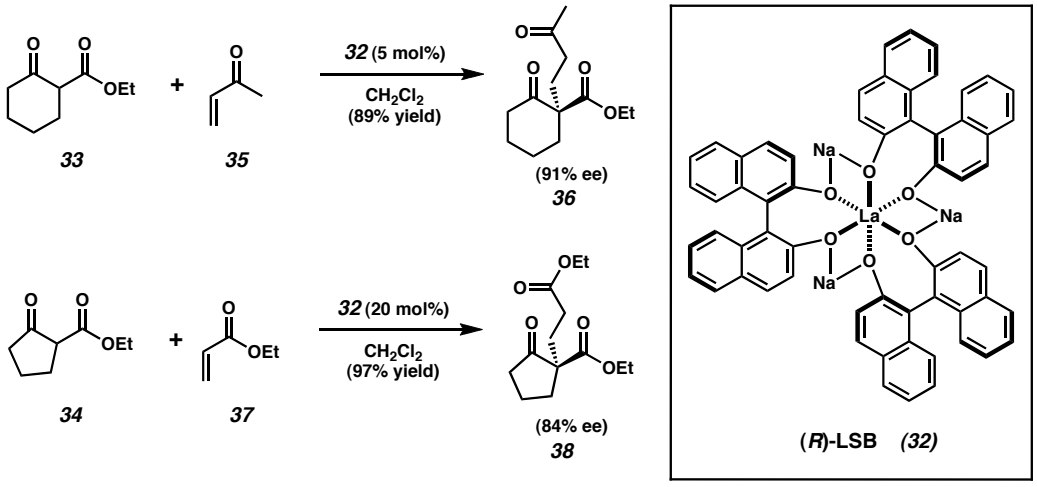
Catalyst	R-group
24	CH_3O
25	CH_3
26	F
27	Cl
28	CF_3

Ion pairing was invoked as the key enantiodetermining interaction. When more polar solvents such as CH_2Cl_2 were substituted for toluene, a drop in enantioselectivity was observed. When substituents R on the catalyst became more electron-withdrawing, a corresponding elevation in ee was observed. A Hammett plot of log (ee/ee_0) versus the σ values for these R-groups gave $\rho = 0.21 \pm 0.02$. A counterion effect of the alkylator was also found. If iodomethane was used instead of chloromethane, there was a decrease in product ee.

1.3.2 *Shibasaki's Lanthanide Sodium Binol Catalyzed Enantioselective Michael Reaction*

Shibasaki demonstrated a catalytic enantioselective direct Michael reaction of β-ketoesters with α,β-unsaturated carbonyls. Using a chiral complex **32** derived from lanthanum and BINOL, highly enantioselective formation of α-quaternary compounds was possible (Scheme 1.5).[20] A few of the reported examples of the direct Michael addition employed cyclic β-ketoesters such as **33** and **34**. Notably, both 5 and 6-membered ring sizes were tolerated. A variety of Michael acceptors including methyl vinyl ketone (**35**) and ethyl acrylate were amenable to the chemistry.

Scheme 1.5 Shibasaki's Direct Michael Reaction

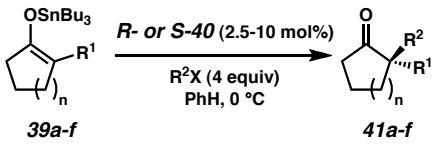


1.3.3 *Jacobsen's Chromium Salen Catalyzed Alkylation*

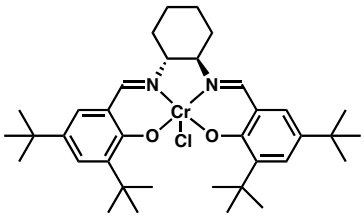
Jacobsen recently reported a catalytic preparation of enantioenriched, α-quaternary cycloalkanones.[21] Readily distilled tri-*n*-butyltin enolates (e.g., **39a-f**) underwent alkylation in the presence of a chromium salen catalyst (***R***- or ***S***-**40**) when treated with activated alkyl iodides and bromides (Table 1.1). A large range of

electrophiles displayed compatibility with the catalyst system, giving rise to a variety of products. 5, 6, and 7-membered ring substrates perform very well in this system, providing a range of cyclic ketones in excellent yield and high ee. The mode of catalyst action is uncertain, but investigations are ongoing.

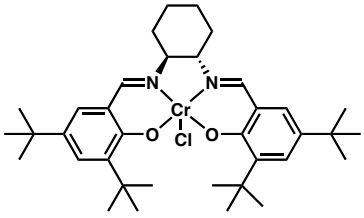
Table 1.1 Enantioselective Alkylation of Tributyl Tin Enolates



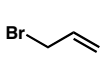
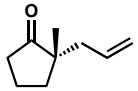
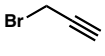
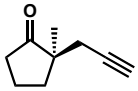
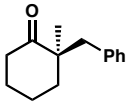
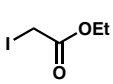
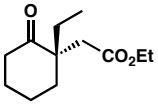
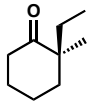
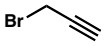
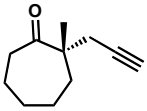
39a-f *41a-f*



(*R,R*)-Salen CrCl (*R-40,* A)



(*S,S*)-Salen CrCl (*S-40,* B)

Entry	R^2X	Catayst	Product	%Yield	%ee
a		A		84	94
b		B		81	96
c		A		67	95
d		B		80	85
e	H_3C-I	B		43	90
f		A		58	92

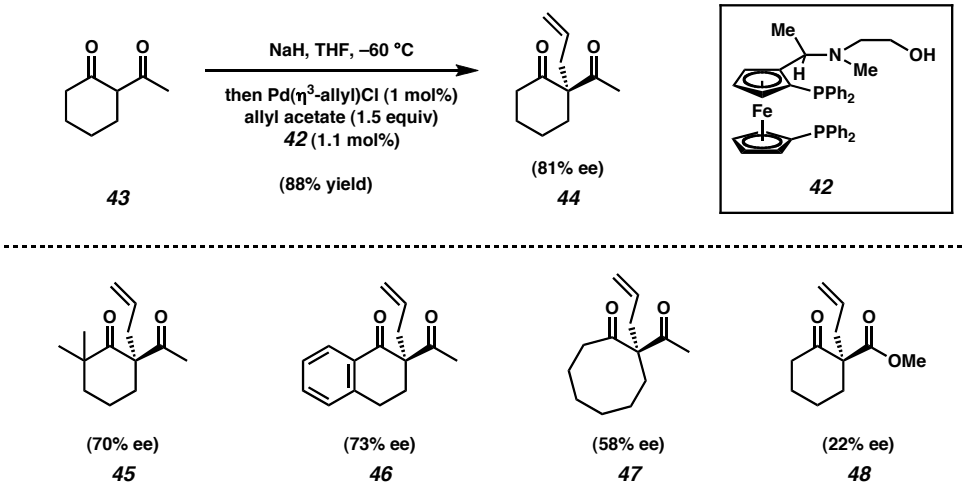
1.4 Palladium Catalysis for Enantioselective Alkylation of Prochiral Enolates

1.4.1 *Hayashi's Allyl Palladium Catalysis*

The attack of prochiral enolates upon η^3-allyl palladium (II) complexes was also recognized as a powerful method for generating all-carbon quaternary stereocenters.

Hayashi pioneered this type of reaction during an exploration of Pd-catalyzed alkylation of β-dicarbonyls (Scheme 1.6).[22] Investigations revealed ferrocenyl catalyst **42** as a superior ligand for the transformation of **43** to **44**. Diverse substrates were screened, and most displayed only limited stereoselectivity. Ultimately, allyl diketone **44** was prepared in a maximum 81% ee. Other activated carbonyl compounds including but not limited to **45**, **46**, **47**, and **48** were also accessible, with modest degrees of enantioselectivity. Optical activity was observed for 7-membered ring substrates, but 5-membered ring examples displayed very low stereoselectivity. Inspired by Hayashi's work, Ito also investigated these enantioselective alkylations using a crown-ether-modified phosphinoferrocenes with modest success.[23]

Scheme 1.6 Hayashi's Enantioselective Alkylation of β-dicarbonyls

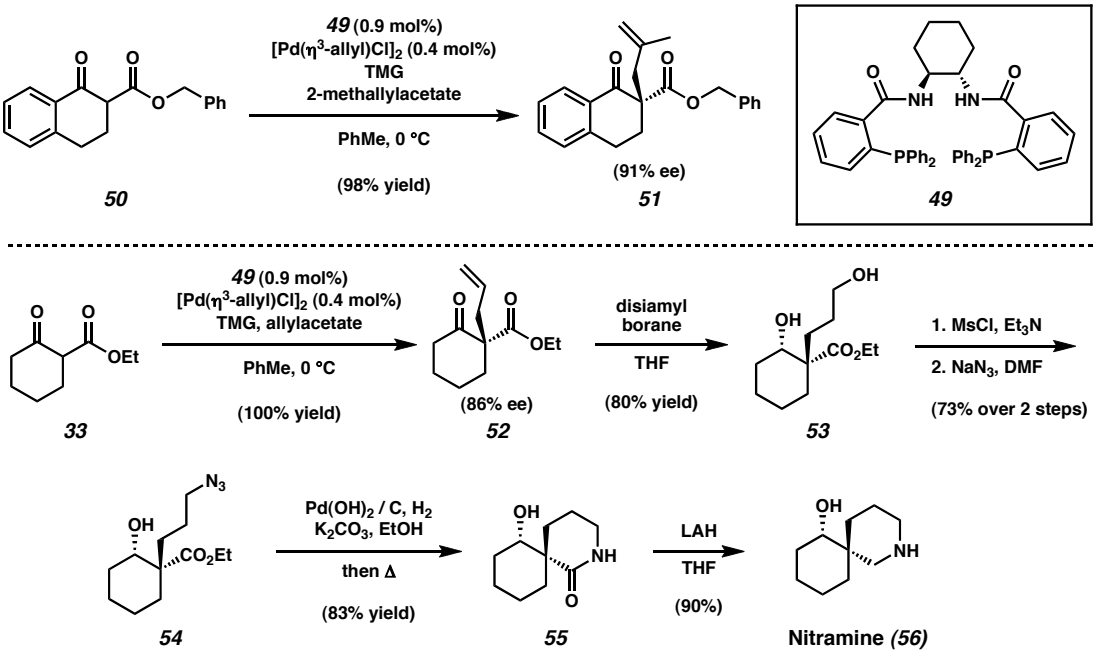


1.4.2 *Early Work by Trost Surrounding Pd-Catalyzed Alkylation*

In an effort to improve the yield, scope, and enantioselectivity of ketone alkylations catalyzed by palladium, Trost developed new ligands (e.g., **49**) designed to

project stereochemical information closer to the site of C–C bond formation (Scheme 1.7).[24] Substrates with a single acidic site could be alkylated in high yield with excellent enantioselectivity. Tetramethyl guanidine (TMG) was more effective than other bases for direct deprotonation. Trost applied this method during a short total synthesis of the alkaloid nitramine (**56**).[24a]

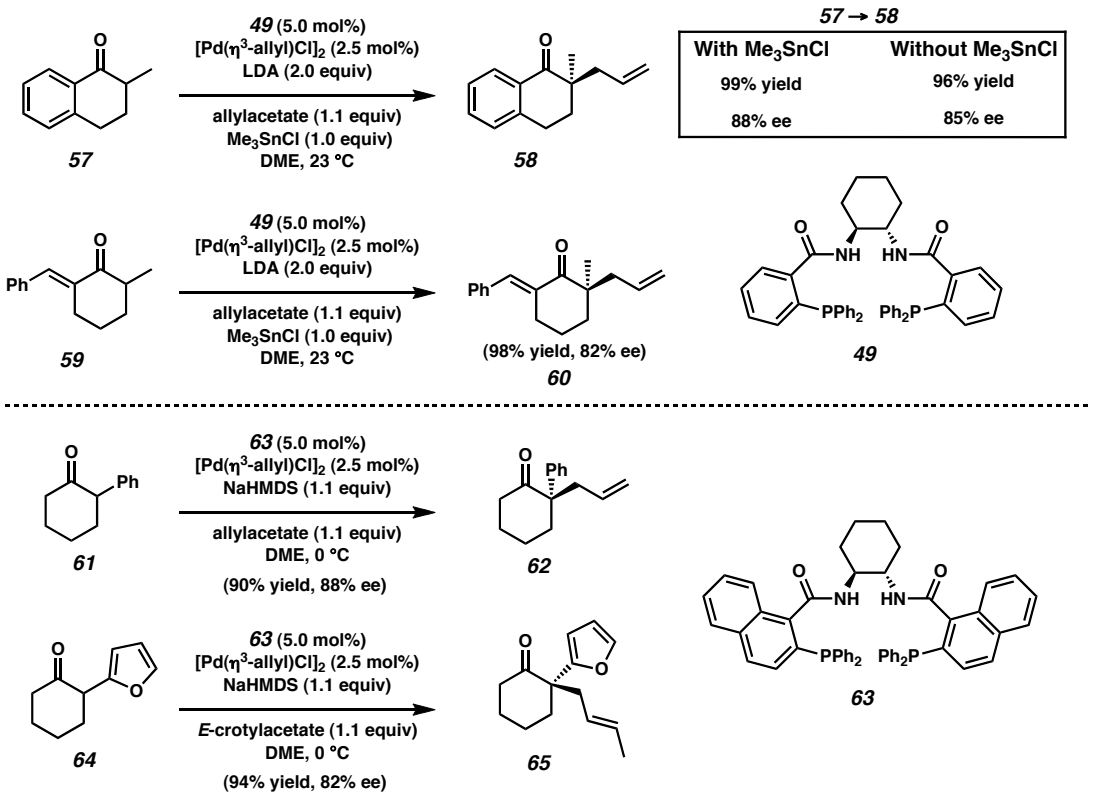
Scheme 1.7 Trost Ligands for Asymmetric Pd-Catalyzed Alkylation



Trost later developed other asymmetric catalyses, allowing the enantioselective alkylation of less acidic substrates. His next system used LDA as a base (Scheme 1.8).[24b] Occasionally, addition of Me_3SnCl to the reaction mixture gave an elevation in ee, although good enantioselectivity could be achieved with LDA alone. Tetralones were ideal substrates for this chemistry because of their single-site acidity. However, alkylidene blocking groups could be installed to prevent enolization at unwanted sites in

non-tetralone examples (e.g. **59**), giving access to α-quaternary cycloalkanones in high ee. Hou and Dai later reported another Pd-catalyzed asymmetric alkylation using ferrocenylphosphines similar to the ones reported by Trost.[25]

Scheme 1.8 Other Substrate Classes Investigated by Trost



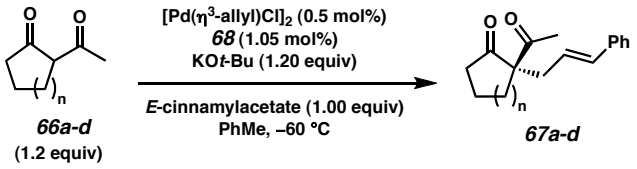
Trost developed another Pd-catalyzed alkylation employing NaHMDS as the base, and α-arylcyclohexanone substrates were investigated (Scheme 1.8). Once again, single-site acidity inherent in the substrate aided regioselective C–C bond formation. 2-Furyl cyclohexanone **64** could be crotylated to give a single olefin isomer of **65** with high yield and stereoselectivity.[24c] Trost's Pd-catalyst manifold was one of the first systems

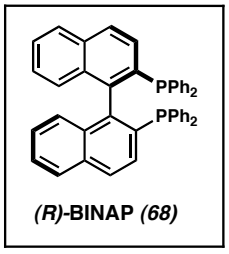
able to install branched and cyclic allyl fragments at the carbonyl α position with high enantioselectivity.

1.4.3 *Ito's BINAP-Pd Catalyst*

Another catalyst system recently described by Ito was capable of building quaternary stereocenters with branched allyl substituents.[26] (*R*)-BINAP (**68**) was used in conjunction with a Pd source. Using *E*-cinnamylacetate, Ito prepared a variety of α-quaternary-β-dicarbonyls (Table 1.2). A great variety of ring sizes were compatible with the chemistry, and enantioselectivities were uniformly in the 70-85% range.

Table 1.2 Enantioselective Cinnamylation of β-Diketones





Entry	n	%yield	%ee
a	1	92	81
b	2	99	85
c	3	95	77
d	4	90	84

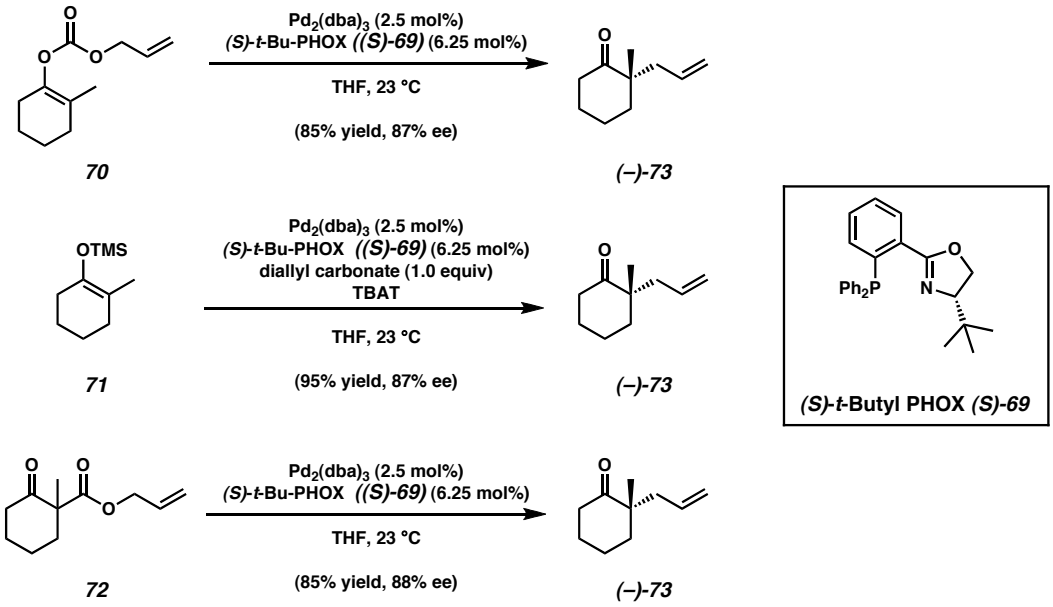
yield base on *E*-cinnamylacetate

1.4.4 *Enantioselective Pd-Catalyzed Decarboxylative Alkylation*

We became interested in the challenge of designing a catalyst system capable of generating all-carbon quaternary stereocenters from cyclic ketones with multiple acidic sites. Three palladium-catalyzed enantioselective decarboxylative alkylations[27] were

developed based on analogous racemic systems reported by Tsuji and Saegusa in the 1980's (Scheme 1.9).[28] Chiral *t*-butyl-phosphinooxazolines (e.g., (*S*)-*t*-Bu-PHOX (***(S)*-69**)) are used in each of the catalyst manifolds, and the electronic and steric features of the ligand are readily modified to enhance reactivity and enantioselectivity.[29]

Scheme 1.9 Three Example of Enantioselective Decarboxylative Alkylation

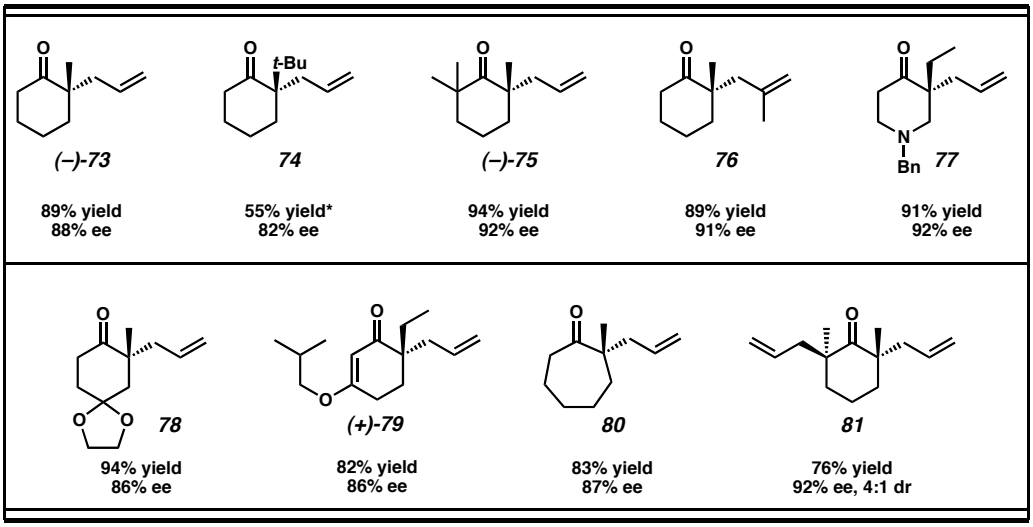


The first method employs allyl enol carbonates such as **70**, wherein the prochiral enolate and allyl fragment are part of the same starting material (Scheme 1.9).[30] A second variation of this catalysis utilizes silyl enol ethers (e.g., **71**) and diallyl carbonate, an external allyl source. The fluoride promoter tetra-*n*-butyl ammonium difluorotriphenylsilicate (TBAT) facilitates desilylation and generation of the prochiral enolate for alkylation.[30] The third asymmetric alkylation involves a stereoablative enantioselective transformation[31] of racemic β-ketoesters. Deallylation of substrate **72**

followed by decarboxylation leads to a prochiral enolate, which is enantioselectively alkylated to generate allyl ketone **(–)-73**.[32]

Many substrate classes were investigated (Table 1.3).[30,32] The substrate can harbor considerable steric congestion near the site of C–C bond formation as evidenced by *t*-butyl ketone product **74**. Steric bulk at other positions is also tolerated (e.g., **(–)-75**). It is also possible to bring in substituents at the 2-position of the allyl fragment (**76**), and heteroatoms can also be part of the substrate (e.g., **77** and **78**). Vinylogous ester substrates (e.g., **79**) and 7-membered rings (e.g., **80**) are also well tolerated by the catalyst system. For the first time, two enantioselective decarboxylative alkylations can be performed sequentially, giving **81** in high ee.

Table 1.3 Substrate Scope of the Enantioselective Decarboxylative Alkylation

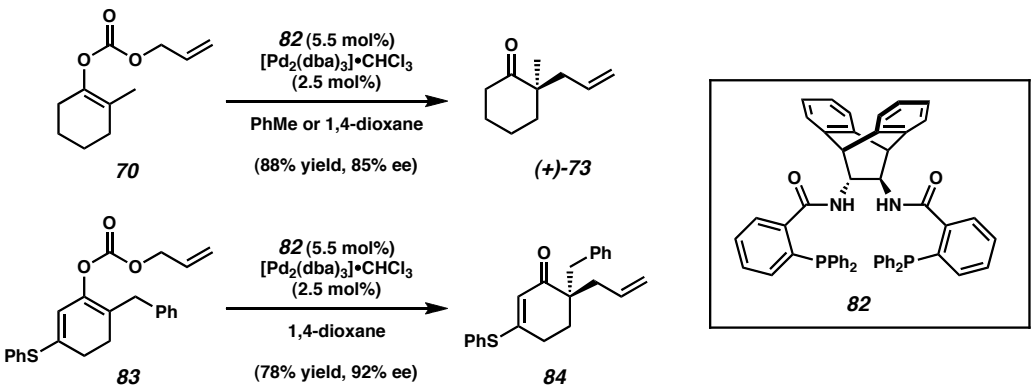


*Yield after Wacker oxidation to the corresponding diketone

1.4.5 *Other Enantioselective Decarboxylative Alkylation Methodologies*

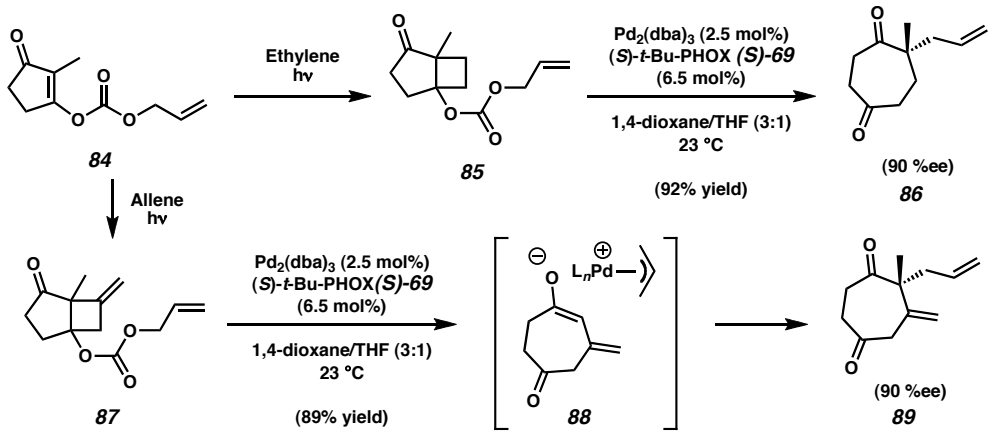
Subsequent to our investigations into Pd-catalyzed decarboxylative alkylation, the Trost lab published a similar technology using ligand **82** (Scheme 1.10).[33] A variety of enantioenriched cyclic all-carbon quaternary ketones and vinylogous thioesters are available using this chemistry. Yields and enantioselectivities are high, and both allyl enol carbonates and allyl β-ketoesters can be used.

Scheme 1.10 Trost's Enantioselective Decarboxylative Alkylations



A clever means to generate the prochiral enolate for enantioselective alkylation was recently reported by Blechert.[34] Enol carbonates such as **84** can undergo [2 + 2] photoaddition with ethylene or allene (Scheme 1.11). Treatment of the bicyclo[3.2.0]heptanes with Pd^0 and (*S*)-*t*-Bu-PHOX (***(S)*-69**) induces a retro-aldol ring expansion. The resulting enolates are enantioselectively alkylated, generating α-quaternary cycloheptanediones. In the case of **87**, the intermediate enolate **88** does not undergo γ-alkylation. Consequently, the exo-methylene group is retained. These transformations represent enantioselective de Mayo reactions.[35]

Scheme 1.11 Blechert's Ring Expansion/Enolate Alkylation Cascade



1.5 Concluding Remarks

Numerous methods have been developed addressing the generation of all-carbon quaternary stereocenters within rings via alkylation. Certain technologies have even been applied to the syntheses of pharmaceuticals and natural products. Early alkylation approaches utilized chiral auxiliaries, but in more recent years catalytic methods have been developed. Among these technologies are the versatile alkylations catalyzed by palladium. Three very powerful methods for generating all-carbon quaternary stereocenters via enantioselective decarboxylative allylation have recently been developed in our labs. Enol carbonates, silyl enol ethers, and β-ketoester substrates can be readily elaborated to α-quaternary ketones. Our goal has been to use these enantioselective Pd-catalyzed alkylations to synthesize biologically relevant natural products with novel skeletal structures.

1.6 Notes and Citations

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