Enantioselective Palladium-Catalyzed Transformations

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Contents

1. Introduction 3453
2. Heck Reactions 3454
   2.1. Intramolecular Heck Reactions 3454
   2.2. Intermolecular Heck Reactions 3462
      2.2.1. 2,3-Dihydrofurans and Cyclic Enol Ethers 3462
      2.2.2. Intermolecular Arylation and Alkenylation of Dihydropyrroles 3468
      2.2.3. Intermolecular Arylation and Alkenylation of Alkenes 3469
3. Hydroarylation/Alkenylation of [2.2.1]Bicycles 3471
4. Carbopalladation–Addition/Cyclization of Allenes 3472
5. Enyne Cycloisomerizations 3474
6. Carbonylation and Cyclocarbonylation Reactions 3478
7. Cycloaddition Reactions 3483
   7.1. Diels–Alder Reactions 3483
   7.2. Hetero-Diels–Alder Reactions 3485
   7.3. [3+2] Dipolar Cycoadditions 3486
   7.4. [3+2] Cycloadditions of Vinyloxiranes with Heterocumulenes 3486
8. Addition of Carbon Nucleophiles to C═O, C═N, and Activated C═C Bonds 3488
   8.1. Nucleophilic Addition to C═O Bonds 3488
   8.2. Nucleophilic Addition to C═N Bonds 3489
   8.3. Michael Additions 3491
9. Cross-Coupling Reactions 3492
   9.1. Kumada-Type Cross-Couplings 3492
   9.2. Suzuki-Type Cross-Couplings 3494
10. Arylation of Ketone Enolates 3495
11. Other C–C Bond-Forming Reactions 3497
   11.1. Alkylative Ring Opening of Oxabicycles 3497
   11.2. Synthesis of Axially Chiral Allenes 3498
   11.3. Hydrocarbonation of Allenes 3499
12. Hydrosilylations 3500
   12.1. Hydrosilylation of Alkenes and Alkynes 3500
   12.2. Cyclization–Hydrosilylation of Functionalized 1,6-Dienes 3503
13. Hydroamination of 1,3-Dienes 3504
14. Fluorination of β-Ketoesters 3505
15. Wacker-Type Oxidation and Oxidative Cyclization 3506
16. Hydrogenation of Imines 3509
17. Miscellaneous Transformations 3510
18. Conclusion 3510
19. Addendum 3511
20. List of Abbreviations 3511
21. Acknowledgment 3512
22. References 3512

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1. Introduction

Palladium-catalyzed transformations have seen a fascinating development in recent years after being for a long time in silence as a "sleeping beauty".[1] The importance of Pd in synthesis is evident from the huge number of name reactions in connection with this field. The great advantage of Pd-catalyzed processes in the formation of C−C, C−O, C−N, and even C−S bonds is the mildness of most of these processes, tolerating many functional groups. Moreover, these catalytic processes help researchers obey the rules of ecological awareness.[2] A further powerful extension, also of economical interest, is the development and use of multiple Pd-catalyzed transformations which may be performed in a domino fashion.[2c,3]

So far the best known Pd^0-catalyzed transformations are the arylation and alkenylation of alkenes, the cross-coupling of alkynes as well as of boron, silicon, and tin compounds, and the hydrogenation and nucleophilic substitution of allylic carbonates or acetates. However, this now has been greatly extended to cycloisomerization, hetero- and carboannulation, Michael additions, nucleophilic addition to C═O and C═N bonds, and pericyclic reactions as well as fluorination, hydroamination, and hydrosilylation. An industrially important process using Pd^{II} is the Wacker oxidation of alkenes to give aldehydes.

Moreover, a breakthrough in Pd-catalyzed transformations has been achieved with the development of enantioselective transformations: ee values of over 95% are now more the rule than the exception. Thus, the design of new, highly potent ligands is an important issue. The first investigations in this field were on enantioselective Heck reactions by Overman[4] and Shibasaki,[5] cross-coupling reactions by Hayashi,[6] copolymerization of alkenes and CO by Nozaki,[7] and nucleophilic substitutions by Trost and van Vranken.[8]

It is the purpose of the present review to highlight the most important progress in enantioselective Pd-catalyzed transformations in the past few years. However, we did not include enantioselective Pd-catalyzed nucleophilic substitutions due to the huge amount of publications in this field covering *C*-

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Lutz F. Tietze (right, born 1942 in Berlin, Germany) studied chemistry at the universities of Kiel and Freiburg and received his Ph. D. in organic chemistry in 1968 under the guidance of B. Franck. After postdoctoral stays with G. Büchi at the Massachusetts Institute of Technology, Cambridge, MA, and A. R. Battersby in Cambridge, UK, he finished his habilitation in 1975 at the University of Münster. In 1977 he was appointed professor at the University of Dortmund and one year later at the University of Göttingen, where he is still today. Tietze has been a visiting professor in Madison, Strasbourg, Sydney, Bologna, and Paris. Among his recent honors and awards are the Literature Prize of the Fonds der Chemischen Industrie, an honorary doctor of the University of Szeged (Hungary), the Grignard-Wittig Award of the Société Française de Chimie, and the Emil-Fischer Gold Medal. He is director of the Institute of Organic and Biomolecular Chemistry at the University of Göttingen and a member of the Board of Referees of the Deutsche Forschungsgemeinschaft. Furthermore, he is president of the Deutscher Zentralausschuss für Chemie (Board of the German Chemical Societies). Apart from the development of efficient synthetic methods involving domino processes as well as transition metal catalysis, natural product synthesis, and combinatorial and high-pressure chemistry, his research interests include the development of new anti-cancer agents for a selective tumor therapy using monoclonal antibodies. He has published over 340 papers and about 25 patents, and his book on synthetic organic chemistry, which he wrote with Th. Eicher, has been translated into Chinese, English, Japanese, Korean, and Russian.

Hiriyakkanavar Ila (middle) was born in 1944 in Mathura, India, studied chemistry at DAV College in Kanpur, and received her Ph.D. in chemistry from the Indian Institute of Technology (IIT), Kanpur, in 1968. After a postdoctoral stay with R. L. Whistler at Purdue University, Lafayette, IN (1969), she joined the Central Drug Research Institute, Lucknow, India (1970), as a research scientist. Together with her husband H. Junjappa, also a chemistry professor, she moved to the new North Eastern Hill University, Shillong, in 1977, to establish a school of chemistry there. She became professor in 1986 and joined the Department of Chemistry at the IIT, Kanpur, in 1995, where she is still working today. She has been elected Fellow of the Indian Academy of Science, Bangalore (1990), and Fellow of the Indian National Science Academy, New Delhi (2001). Among her recent honors are the Chemical Research Society of India silver medal (2001) and the A. V. Ramarao foundation prize in chemistry. She has been Alexander von Humboldt Fellow (1984–1985, with R. Gompper in Munich; 1998, 2000, 2001, and 2003 with L. F. Tietze in Göttingen), Marie Curie visiting fellow (1995, with I. Flemming in Cambridge, UK), INSA exchange visitor in UK and France (1993, 1996), and visiting professor (Sevilla, 1999; Los Angeles, 2002). She has been a coauthor of 190 publications in international journals, and her research activities revolve around the design and development of new synthetic methods for biologically important molecules, especially heterocycles and domino reactions.

Hubertus P. Bell (left, born 1976 in Aachen, Germany) studied chemistry at the University of Göttingen and at the Ecole Nationale Supérieure de Chimie de Paris (ENSCP), accomplishing his diploma under the guidance of L. F. Tietze, with a thesis on the "Synthesis of a haptene for a novel immunotherapy of tumors". He finished his Ph. D. on "Palladium-catalyzed domino cyclizations for an efficient synthesis of tetracycline antibiotics" in January 2004, and is currently working together with Prof. Tietze on a book about domino reactions. He is co-editor of a cookbook, *What's Cooking in Chemistry?* (Wiley-VCH, 2003), and recipient of doctoral scholarships of the Studienstiftung des deutschen Volkes (German Merit Foundation) and the Fonds der chemischen Industrie.

allylation,[9] *N*-allylation,[10] *O*-allylation,[11] and *S*-allylation[12] as well as reduction[13] and the creation of quaternary stereogenic centers.[14] Including all of that work would have broken the limits of this review, and the reactions have recently been discussed in depth.[1]

However, it is important to note that in this review we have included several enantioselective Pd-catalyzed transformations which have never been reviewed before. Thus, besides the enantioselective Heck and cross-coupling reactions, also pericyclic reactions, aldol additions, hydrosilylations, hydroarylations, and several other transformations including enantioselective Pd^{II}-catalyzed processes are described.

The literature from 1996 to 2002 has been covered thoroughly, and some important references from 2003 have also been included. Some excellent reviews on selected enantioselective Pd-catalyzed transformations have already appeared which cover the earlier literature.[15]

2. Heck Reactions

From its modest beginnings in the late 1980s, the enantioselective Heck reaction[16−18] and especially its intramolecular version, first reported by Shibasaki[19] and Overman,[20] has emerged as one of the most powerful methods for the enantioselective formation of both tertiary and quaternary stereogenic centers in polyfunctional molecules. This has led to its wide application in the synthesis of many complex natural products.[15c,17a−d] Two recent review articles by Shibasaki[17a] and Overman[17b] have covered this topic up to 1999, focusing especially on the intramolecular Heck reaction. Here, a detailed description of intermolecular enantioselective Heck reactions which have not been highlighted earlier will be given; in addition, important developments in this field in recent years are discussed.

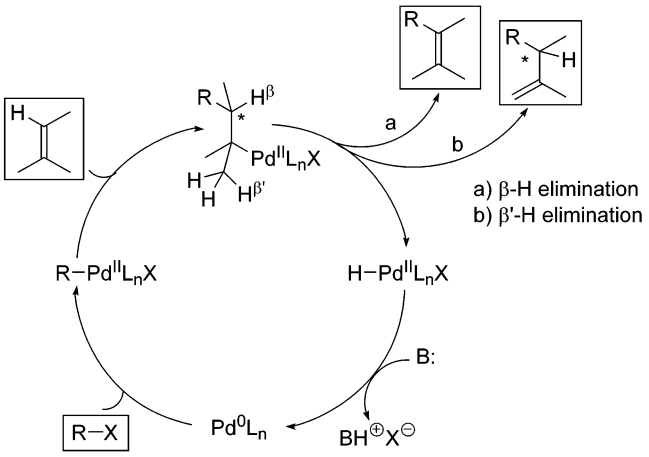
2.1. Intramolecular Heck Reactions

The general outlines of the mechanism of the Heck reaction[21,22] and the factors governing the regio- and enantiocontrol[23] of the reaction have been discussed in several reviews.[17a−e] Because of the major limitation that the Heck reaction displays low regioselectivity in the double bond formation step, all the reported enantioselective Heck reactions leading to the formation of tertiary centers have been done on cyclic alkenes, with the exception of Tietze's allylsilane-terminated enantioselective Heck reaction (vide infra).[24] Using cyclic alkenes in the Heck reaction, the syn elimination of $HPdL_2$ from the first formed syn adduct can only take place in one direction since the otherwise necessary σ-bond rotation is not possible in cyclic alkenes (Scheme 1).

Shibasaki and co-workers have carried out pioneering work[19] in this field, applying Heck reactions for the enantioselective synthesis of fused ring systems such as decalins[19,25] (eq 1), hydrindans[26] (eq 2), indolizidines[27] (eq 3), diquinanes[28] (eqs 5 and 6), and the related natural products.

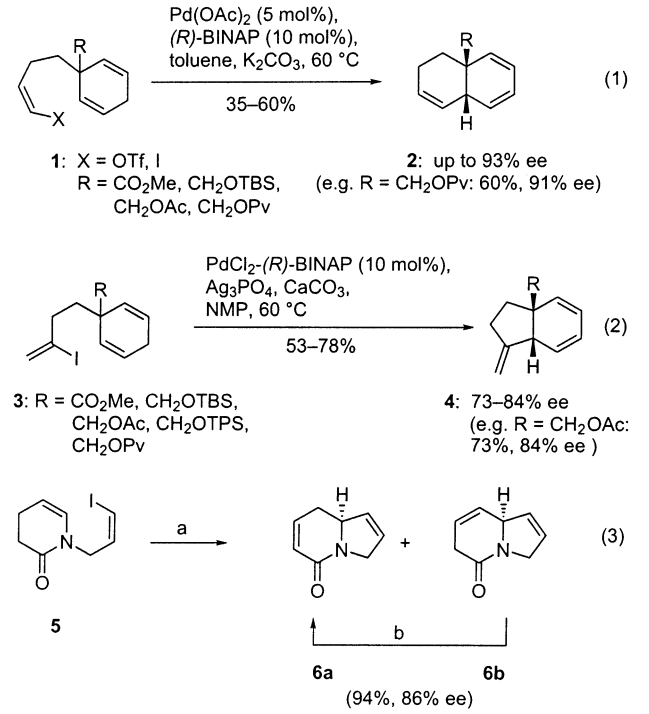
By careful optimization of the anionic components of both palladium sources, more particularly the silver salts and reaction conditions, the products

Scheme 1. Mechanism of the Asymmetric Heck Reaction

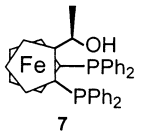


could be obtained in high yields with ee values between 80 and 91%. (*R*)-BINAP proved to be the chiral ligand of choice in most of the enantioselective Heck reactions studied, although (*R*)-α-[(*S*)-1′,2-bis-(diphenylphosphino)ferrocenyl]ethyl alcohol (BPPFOH, **7**) was found to be most effective for the formation of indolizidines[27] from the vinyl halide **5** (eq 3). Recently the new ligand 2,2′-bis(diphenylarsino)-1,1′-binaphthyl (BINAs, **8b**), introduced by the same workers,[25b] has been shown to be superior to (*R*)-BINAP for the conversion of vinyl iodides **1** (X = I) to **2**, with an optimized yield of 90% and 82% ee (**2**, R = CH_2OTBS). However, BINAs is a much less effective ligand in intramolecular Heck reactions of aryl and alkenyl triflates.

In a more significant extension, Shibasaki and co-workers have reported the synthesis of several enones and dienones,[29] including the key intermediate **11**,[30]



a) $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mol% Pd), *(R)-(S)*-BPPFOH 7 (9.6 mol%), Ag-exchanged zeolite, $CaCO_3$, DMSO/DMF, 0 °C
b) Pd/C, MeOH, 23 °C, quant.



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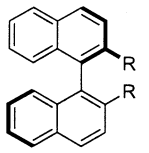
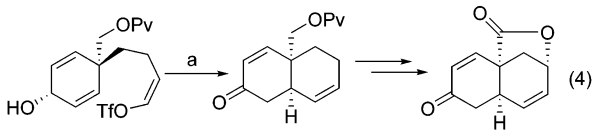


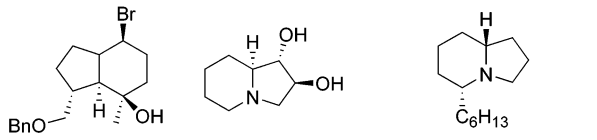
8a: *(R)*-BINAP (R = PPh_2)
8b: *(R)*-BINAs (R = $AsPh_2$)
8c: *(R)*-tolBINAP (R = P(4-MeC_6H_4)$_2$)

an intermediate in Danishefsky's synthesis of vernolepin,[31] via an enantioselective Heck reaction on divinyl alcohol **9** (eq 4).



9 **10**: 76%, 86% *ee* **11**

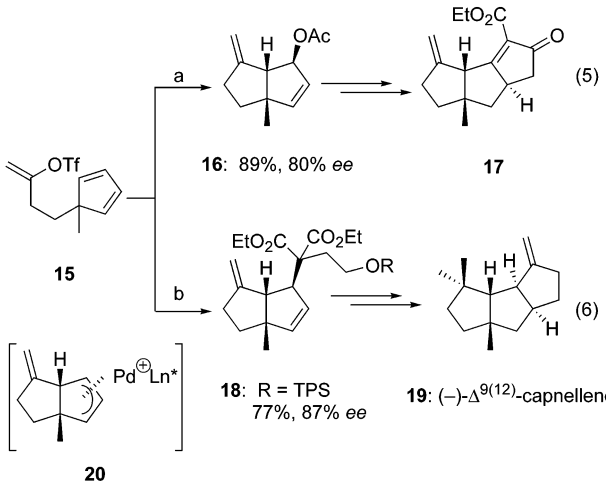
a) $Pd_2(dba)_3{\cdot}CHCl_3$ (9 mol% Pd), (*R*)-BINAP(11.3 mol%), K_2CO_3, *t*BuOH, $ClCH_2CH_2Cl$, 60 °C, 3 d



12 **13**: (+)-lentiginosine **14**: (−)-gephyrotoxin 209D

Similarly, the hydrindan **4** (R = CH_2OTBS) was subsequently converted by the same group into **12**,[32] which is a key intermediate in the synthesis of (−)-oppositol and (−)-prepinnaterpene.[33] These workers have also reported the synthesis of the naturally occurring alkaloids lentiginosine **13**, 1,2-diepilentiginosine, and gephyrotoxin 209D **14** utilizing the indolizidine precursor **6** (eq 3).[34]

In a subsequent extension of the method, Shibasaki and co-workers successfully employed an enantioselective Heck reaction for the formation of diquinane systems[28] (eqs 5 and 6) present in a wide range of important natural products. The overall process



a) $Pd(OAc)_2$, (*S*)-BINAP, Bu_4NOAc, DMSO, 25 °C, 2.5 h
b) $[Pd(allyl)Cl]_2$ (2.5 mol%), (*S*)-BINAP (6.3 mol%), NaBr, $(CO_2Et)_2(CNa)(CH_2)_2OTPS$, DMSO, 25 °C

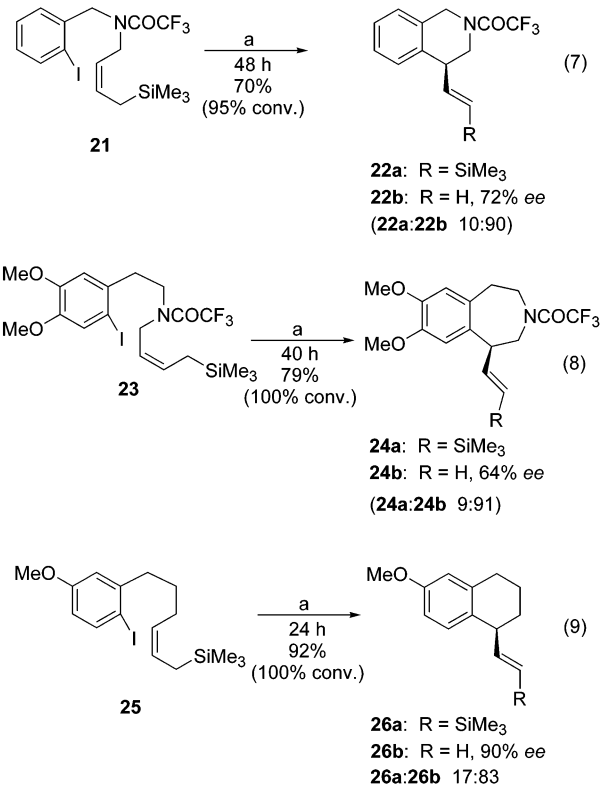
involves the generation of the π-allylpalladium intermediate **20** from the cyclopentadiene substrate **15** and its trapping by a suitable nucleophile such as tetrabutylammonium acetate, yielding diquinane

Table 1. Enantioselective Silane-Terminated Heck Reaction of Allylsilanes 32 and 35 (Eqs 11 and 12)

entry	substrate	product	catalyst (mol %)	ligand (mol %)	yield (%) a	yield (%) b	ee (%) a	ee (%) b
1	**32a** (*Z*)	**33a**:**34a**	1.5	**30** (15)		71		92 (*S*)
2	**32b** (*Z*)	**33b**:**34b**	3	**30** (15)	6	71		70 (*S*)
3	**32c** (*E*)	**33a**:**34a**	1.5	**31** (10)	66	21	91 (*S*)	60 (*S*)
4	**35a** (*E*)	**36a**:**37a**	3	**30** (15)	25	43	12 (*R*)	64 (*R*)
5	**35b** (*E*)	**36b**:**37b**	3	**30** (10)	9	56	76 (*R*)	56 (*R*)
6	**35c** (*Z*)	**36a**:**37a**	1.5	**30** (15)		61		86 (*S*)
7	**35d** (*Z*)	**36b**:**37b**	1	**30** (20)		73		84 (*S*)

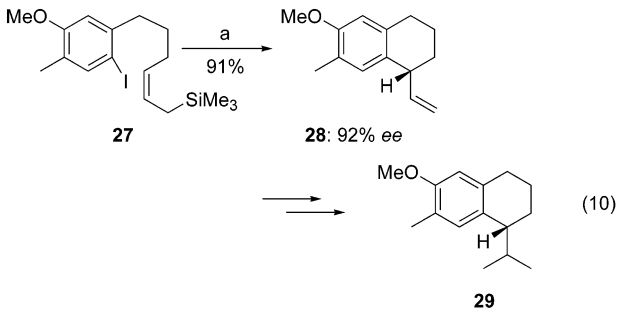
16 with 80% ee in 89% chemical yield. The intermediate **16** was transformed into the triquinane **17**, an intermediate in the synthesis of $\Delta^{9(12)}$-capnellene **19**.[35] Subsequently, Shibasaki and co-workers developed the first catalytic asymmetric synthesis of $\Delta^{9(12)}$-capnellene **19**[36] by trapping the π-allylpalladium intermediate **20** with a β-dicarbonyl carbanion nucleophile to give **18** in 77% yield (87% ee) (eq 6).

Tietze and co-workers have recently shown that one of the main disadvantages of the Heck reaction, namely the low regioselectivity in the Pd−β-hydride elimination step to form the double bond, can be overcome by using an allylsilane[24a] as the terminating alkene component; this allowed, for the first time, the regioselective formation of tertiary stereogenic centers from acyclic alkenes. By careful choice of the reaction conditions and the catalyst, either a vinyl- or a trimethylsilyl-substituted carbocycle could be prepared. Under enantioselective Heck conditions using [$Pd_2(dba)_3$]−(*S*)-BINAP, the vinyl-substituted products were formed predominantly, with an enantiomeric excess as high as 90% in the case of tetralin **26b** (eqs 7−9).



a) $Pd_2(dba)_3$ (2.5 mol%), (*S*)-BINAP (7 mol%), Ag_3PO_4, DMF, 75–80 °C

This allylsilane-mediated enantioselective Heck reaction has been successfully applied by Tietze and his group for the synthesis of the sesquiterpene 7-demethyl-2-methoxycalamene **29** (eq 10).[37]

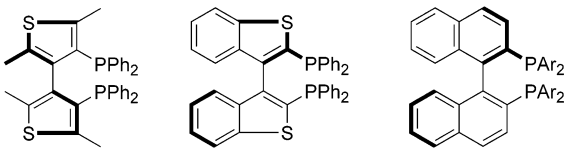


a) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), (*R*)-BINAP (7 mol%), Ag_3PO_4, DMF, 80 °C, 48 h

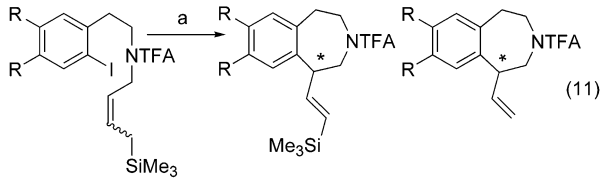
Thus, treatment of the allylsilane **27** with $Pd_2(dba)_3$−(*R*)-BINAP as catalyst in the presence of Ag_3PO_4 gave the desired vinyl-substituted tetrahydronaphthalene **28** in 91% yield with 92% ee, which clearly demonstrates the significance of the allylsilane moiety in enantioselective Heck reactions. With simple alkenes, a mixture of all possible double bond isomers would have been formed. The vinylnaphthalene **28** was subsequently converted into **29** in three steps, involving hydroxylation of the double bond, transformation into *p*-toluenesulfonate, and methylation with Me_2CuLi in 36% overall yield.

The problem of low enantioselectivity observed in the formation of chiral heterocyclic compounds such as tetrahydroisoquinolines **22** (eq 7) and the benzazepines **24** (eq 8) was subsequently overcome by Tietze and co-workers in a recent report[38] employing the new chiral ligands (+)-TMBTP **30** and (*R*)-BITIANP **31** in the enantioselective Heck reaction of (*E*)- and (*Z*)-allylsilanes **32** and **35** (eqs 11 and 12). Thus, the intramolecular enantioselective Heck cyclization of the (*Z*)-iodoarylsilane **32a** in the presence of chiral ligand **30** gave the vinyl-substituted benzazepine **34a** in 71% yield and 92% ee (entry 1, Table 1), whereas the silylvinylbenzazepin **33a** was formed as the major product from (*E*)-**32c** in 60% yield and 91% ee in the presence of chiral ligand (*R*)-BITIANP **31** (entry 3).

In a similar way, (*Z*)-**35c** and (*Z*)-**35d** were transformed in the presence of (+)-**30** into the vinyl-substituted tetrahydroquinolines **37a** and **37b** in 86 and 84% ee, respectively, in good yields (entries 6 and 7, Table 1). However, the enantioselective Heck reaction of (*E*)-allylsilanes **35a** and **35b** gave only low regio- and enantioselectivities (entries 4 and 5, Table

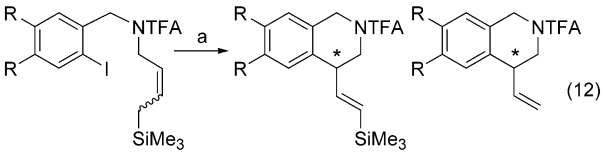


30: (*S*)-(+)-TMBTP **31**: (*R*)-BITIANP **8a**: Ar = Ph, (*R*)-BINAP
8c: Ar = 4-MeC_6H_4, (*R*)-tolBINAP



(11)

32a: (*Z*), R = OMe **33a**: R = OMe **34a**: R = OMe
32b: (*Z*), R = H **33b**: R = H **34b**: R = H
32c: (*E*), R = OMe
32d: (*E*), R = H



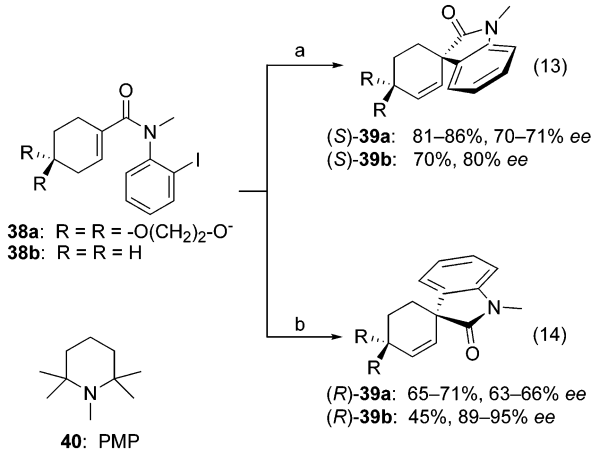
(12)

35a: (*E*), R = H **36a**: R = H **37a**: R = H
35b: (*E*), R = OMe **36b**: R = OMe **37b**: R = OMe
35c: (*Z*), R = H
35d: (*Z*), R = OMe

a) $Pd_2(dba)_3{\cdot}CHCl_3$, L*, Ag_3PO_4, DMF, 80–90 °C, 20–68h

1). These results, together with the investigation on intermolecular enantioselective Heck reactions (section 2.2), have clearly demonstrated that the novel ligands **30** and **31** are superior to other ligands, at least in the transformations presently investigated.

Overman and co-workers have reported the first successful example of creating a quaternary carbon center by an asymmetric intramolecular Heck cyclization.[20,39] The full potential of the reaction became evident in their subsequent studies on the synthesis of enantioenriched 3,3-disubstituted oxindoles by asymmetric Heck cyclization of a series of 2-iodoanilides (eqs 13−16).[40]



(13)

(*S*)-**39a**: 81–86%, 70–71% *ee*
(*S*)-**39b**: 70%, 80% *ee*

38a: R = R = -O$(CH_2)_2$-O-
38b: R = R = H

(14)

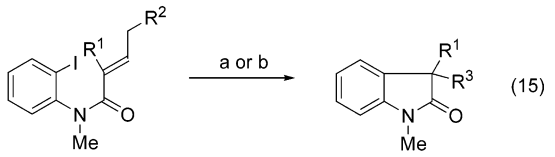
(*R*)-**39a**: 65–71%, 63–66% *ee*
(*R*)-**39b**: 45%, 89–95% *ee*

40: PMP

a) $Pd_2(dba)_3$ (5 mol%), (*R*)-BINAP (11 mol%), Ag_3PO_4, DMA or NMP, 60–80 °C
b) $Pd_2(dba)_3$ (10 mol%), (*R*)-BINAP (22 mol%), PMP, DMA or NMP, 100–110 °C

On the basis of their earlier studies and the recent detailed investigations[41,42] on the effects of a chiral diphosphine structure, the method of catalyst generation, the reaction solvent, and the HI scavenger, Overman and co-workers revealed the most provocative result of their studies that either enantiomer of a Heck product can be obtained using the same enantiomer of the chiral ligand. Thus, the Heck cyclization of the cyclic α,β-unsaturated 2-iodoanilides **38a**,**b**[41] using Pd−(*R*)-BINAP produced the (*S*)-enantiomer of the oxindole **39a**,**b** when the HI acceptor was Ag_3PO_4 (eq 13) and the (*R*)-enantiomer when the HI scavenger was 1,2,2,6,6-pentamethylpiperidine (PMP, **40**) (eq 14). Moreover, these studies demonstrated that the presence of a halide scavenger is not obligatory for obtaining high enantioselection in (diphosphine)palladium-catalyzed enantioselective Heck reactions with halide substrates, as presumed earlier. These exploratory investigations further emphasized the role of the HX scavenger[25d] in determining both the rate and enantioselectivity in asymmetric Heck cyclizations. Thus, a moderately strong proton base such as Ag_3PO_4 or a tertiary amine base such as PMP must be present to obtain useful catalytic rates, whereas silver salts with weakly basic counterions (OTf^-, NO_3^-, BF_4^-) do not efficiently promote the cyclization.

Similar studies on the asymmetric Heck cyclization of several (*E*)-α,β-unsaturated acyclic 2-iodoanilides, such as **41a**−**c**,[41] catalyzed by Pd−(*R*)-BINAP under both Ag_3PO_4- and neutral base (PMP)-promoted conditions (eq 15) also revealed the formation of the opposite enantiomers (**42a** and **43a**, with the exception of **43b**), although the ee's of (*R*)-**42a** and **43a**,**b** obtained using PMP were low.



(15)

(*E*)-**41a**: R^1= Me, R^2= H
(*E*)-**41b**: R^1= Me, R^2= OTBS
(*E*)-**41c**: R^1= *t*Bu, R^2= OTIPS

(*S*) or (*R*)-**42a**: R^1= Me, R^3= CH = CH_2
(*S*) or (*R*)-**43a**: R^1= Me, R^3= CH_2CHO
(*R*)-**43b**: R^1= *t*Bu, R^3= CH_2CHO

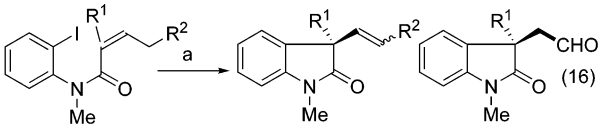
a) $Pd_2(dba)_3$ (5 mol%), (*R*)-BINAP (11 mol%), Ag_3PO_4, DMA, 80–120 °C, 2–27 h
b) $Pd_2(dba)_3$ (10 mol%), (*R*)-BINAP (22 mol%), PMP, DMA, 100–120 °C, 1–2 h

product	yield [%]	*ee* [%]	method
(*S*)-**42a**	88	59	a
(*R*)-**42a**	91	25	b
(*S*)-**43a**	80	45	a
(*R*)-**43a**	85	38	b
(*R*)-**43b**	41	72	a
(*R*)-**43b**	90	27	b

On the other hand, a detailed study[42] on (*Z*)-2-iodoanilides **41a**−**e** in conjunction with (*R*)-BINAP under both sets of conditions gave only the expected (*R*)-enantiomers **42a**−**e** in good yields and with high enantioselection up to 92% (Table 2, eq 16).

Table 2. Enantioselective Heck Cyclization of (*Z*)-41a−e with Pd−(*R*)-BINAP (Eq 16)

substrate	R^1	R^2	additive	(*E*)-**42**: (*Z*)-**42**:**43**	overall yield (%)	overall ee (%)
(*Z*)-**41a**	Me	H	PMP		89	85 (*R*)
(*Z*)-**41a**	Me	H	Ag_3PO_4		85	69 (*R*)
(*Z*)-**41b**	Me	OTBS	PMP	24:1:0	80	92 (*R*)
(*Z*)-**41b**	Me	OTBS	Ag_3PO_4	1:0:1	53	78 (*R*)
(*Z*)-**41c**	*t*Bu	OTIPS	PMP	19:1:0	76	0
(*Z*)-**41c**	*t*Bu	OTIPS	Ag_3PO_4	6:1:0	55	33 (*S*)
(*Z*)-**41d**	Me	OTIPS	PMP	32:1:0	87	90 (*R*)
(*Z*)-**41d**	Me	OTIPS	Ag_3PO_4	4:1:3	73	80 (*R*)
(*Z*)-**41e**	Me	OMe	PMP	9:1:0	76	89 (*R*)
(*Z*)-**41e**	Me	OMe	Ag_3PO_4	4:1:0	72	80 (*R*)

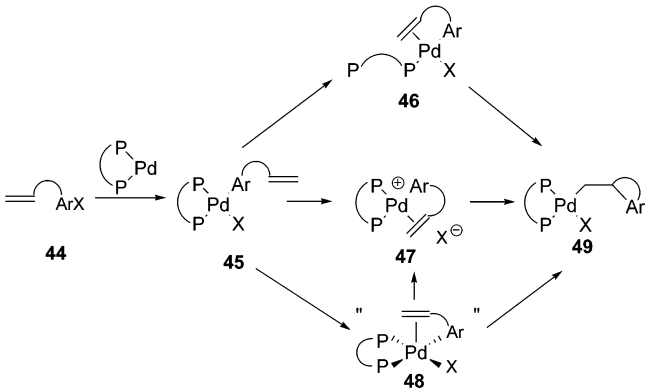


(*Z*)-**41a–e** (*R*)-**42a–e** (*R*)-**43a**: R^1= Me (*R*)-**43b**: R^1= *tBu*

a) $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), (*R*)-BINAP (12 mol%), PMP or Ag_3PO_4, DMA, 100 °C

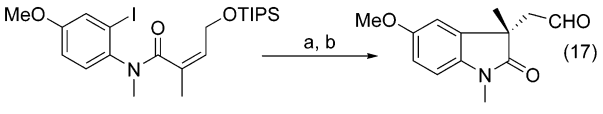
Thus, on the basis of a comparison of the above results, these workers lead to the following conclusion: (*E*)- and (*Z*)-α,β-unsaturated-2-iodoanilides give opposite enantiomers of the Heck products when Ag_3PO_4 is the proton scavenger (cationic pathway), while the sense of stereoselection is independent of the alkene's geometry when the HI acceptor is PMP (neutral pathway). In the same paper,[42] Overman and co-workers reported a number of studies aimed at clarifying the mechanism of the neutral pathway (Scheme 2). On the basis of the low enantioselection

Scheme 2. Proposed Mechanistic Pathway for Neutral Heck Reactions



observed with monophosphine analogues of BINAP designed to mimic a partially dissociated chelate (supporting the conclusion that BINAP is chelated during the enantioselective step) and the insensitivity of the enantioselectivities toward solvent polarity, they have postulated a reaction pathway involving the neutral pentacoordinated palladium intermediate **48**, in which the stereodetermining step occurs during the process where the halide is displaced by the tethered alkene (**45**−**48**−**47**) (Scheme 2). However, these authors state that the sequence **45**−**48**−**47** is an oversimplification of the process, which is much more complicated, and it is vastly premature to advance a three-dimensional model to rationalize stereoinduction in the asymmetric Heck reactions that proceed via a neutral pathway. Nonetheless, the important finding that the asymmetric Heck reactions that proceed via a neutral pathway involve five-fold-coordinated intermediates broadens the vista for the design of these asymmetric ligands for this and related reactions.

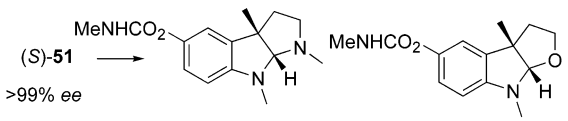
Subsequently, Overman and co-workers have demonstrated the utility of this asymmetric Heck methodology by enantioselective total synthesis of the calabar alkaloids (−)-physostigmine **52** and (−)-physovenine **53** and their enantiomers through catalytic Heck cyclization. In the key step, (*Z*)-2-methyl-2-butenanilide **50** was transformed into the oxindole aldehyde (*S*)-**51** (84% yield, 95% ee) (eq 17).[39b,43]



50 **51**

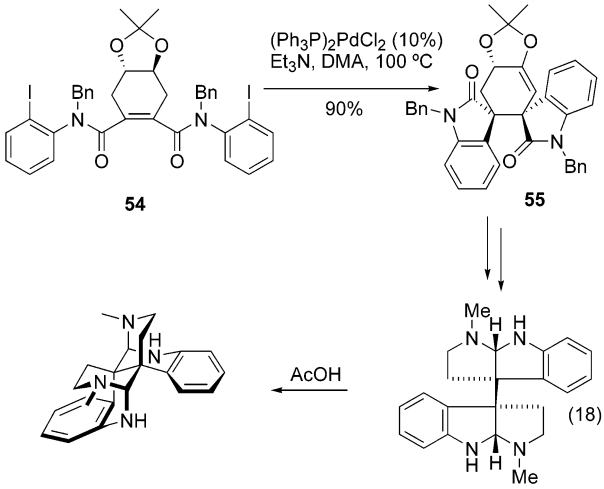
(*S*)-**51**, 84% from 41, 95% *ee* (99% *ee* after recryst.)

a) $Pd(dba)_3{\cdot}CHCl_3$ (10 mol%), (*S*)-BINAP (23 mol%), PMP, DMA, 100 °C
b) 3M HCl, 23 °C



52: (−)-physostigmine **53**: (−)-physovenine

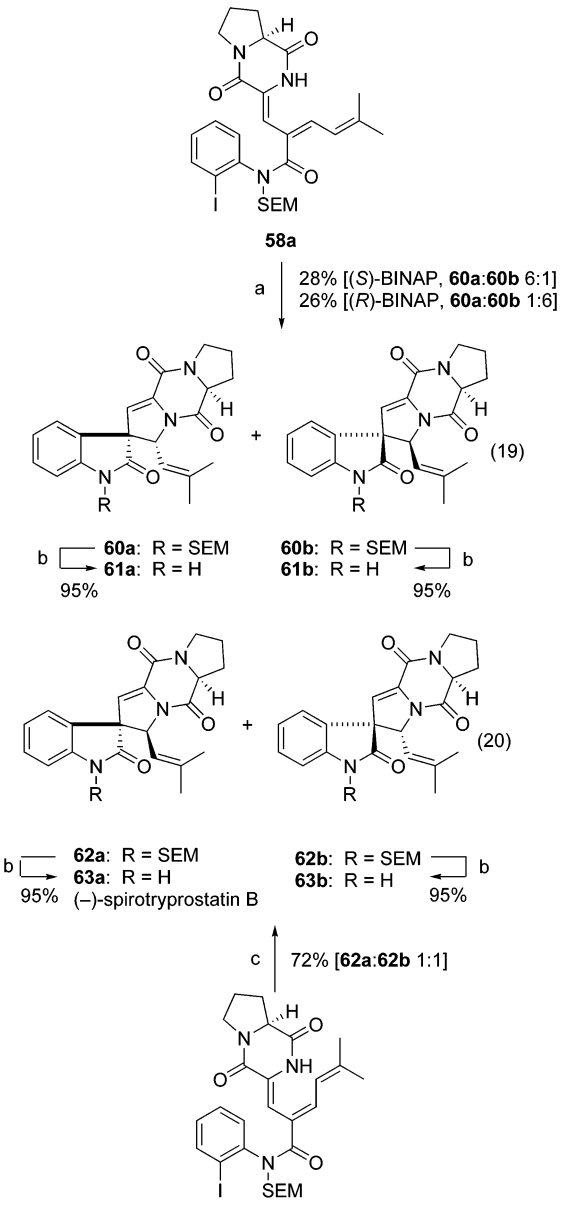
Also worth mentioning at this juncture are the two elegant syntheses reported recently by Overman involving a stereo- and enantioselective route for the synthesis of hexacyclic chiral 3a,3a′-bispyrrolo[2,3-*b*]indolines[44a] (i.e., (−)-chimonanthine, **57**) and their calycanthine isomer **56** via an intramolecular double Heck cyclization of the intermediate **54**, forging two vicinal quaternary centers to give the pentacyclic bisoxindole **55** in high yield and with complete stereocontrol (eq 18).



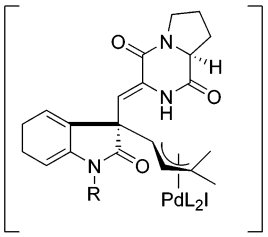
56: (+)-calycanthine **57**: (−)-chimonanthine

The bisoxindole **55** was converted to (−)-chimonanthine in 67% overall yield, which on exposure to acetic acid provided (+)-calycanthine **56** in 60% yield (eq 18). Recently the same group has reported an elegant synthesis of (−)-spirotryprostatin B **63a**[44b] and

its three stereoisomers (**61a**, **61b**, and **63b**), involving the stereocontrolled construction of a quaternary spirocenter and an adjacent stereocenter through a domino intramolecular Heck insertion of a conjugated triene (**58a** or **58b**) and trapping of the resulting η^3-allylpalladium intermediate **59** intramolecularly by the nitrogen of a tethered diketopiperazine which proceeds with anti stereochemistry (eqs 19 and 20).[44b]



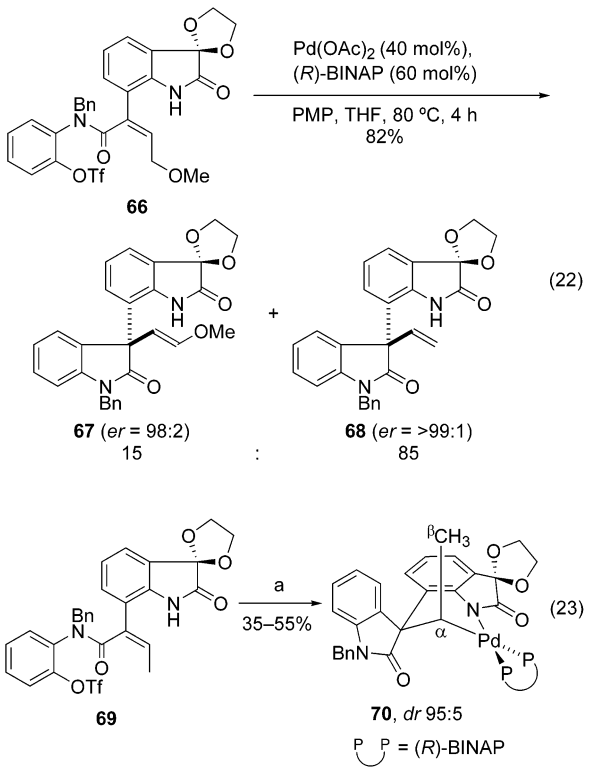
a) $[Pd_2(dba)_3]\cdot CHCl_3\cdot$(*R*) or (*S*)-BINAP (20%) PMP, DMA, 100 °C
b) Me_2AlCl, *i*Pr_2NEt
c) $[Pd_2(dba)_3]\cdot CHCl_3$ (10%) (*o*-tol)$_3$P (40%), KOAc, THF, 70 °C



59

Remarkable diastereoselectivities have also been observed by Grigg and co-workers in the intramolecular asymmetric Heck reaction of amide **64** with RAMP or SAMP as chiral auxiliaries, which afforded one single diastereoisomer of **65** (eq 21).[45]

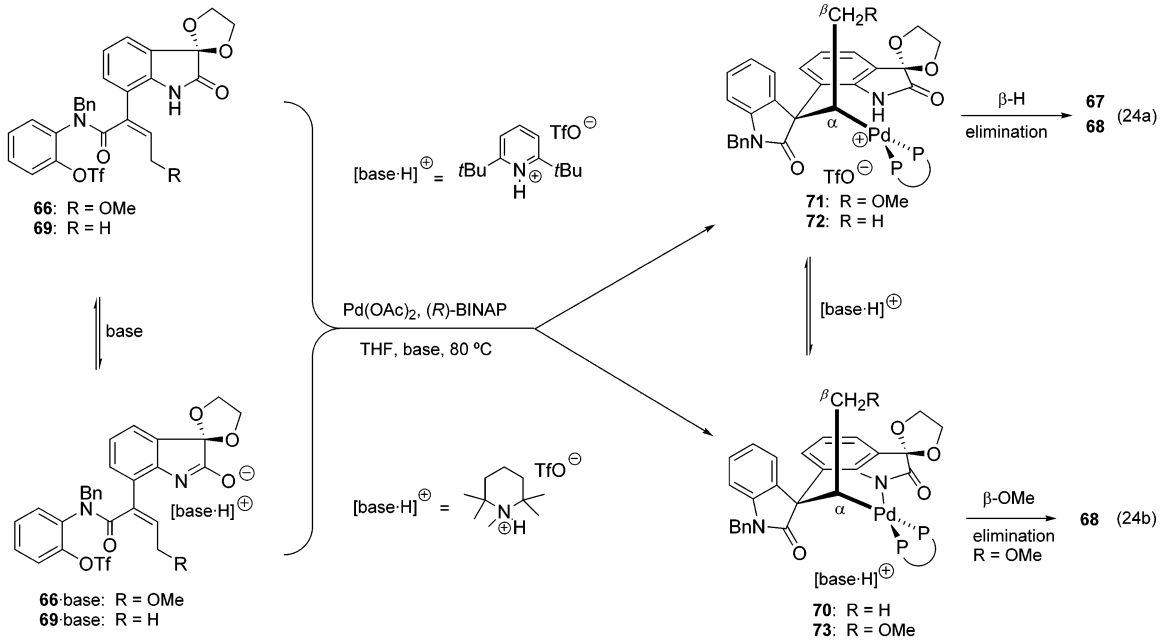
During the studies directed toward the enantioselective total synthesis of tetrameric members of the polypyrrolidinoindoline alkaloid family (i.e., quadrigemine C), Overman et al.[46] investigated the intramolecular asymmetric Heck cyclization of substrate **66** under basic (PMP) conditions, which gave a mixture of two Heck products (**67** and **68)** with the formation of the expected Heck product **67** only in a minor amount (eq 22).



a) $Pd(OAc)_2$ (1.0 eq), (*R*)-BINAP (1.5 eq), PMP, THF, 80 ºC, 4 h

The major product was found to be **68**, a compound resulting from a β-methoxide rather than a β-hydride elimination. The quaternary carbon centers of both of the oxindoles **67** and **68** were formed in high enantiomeric excess (96 and >98%, respectively) (eq 22). Interestingly, the similar asymmetric Heck cyclization of the corresponding demethoxy derivative **69** in the presence of excess $Pd(OAc)_2$ (100 mol %), (*R*)-BINAP (150 mol %), and PMP as base afforded a stable palladium-containing compound in good yield, identified as the palladacycle **70** (eq 23). This unusual palladium complex **70** was found to be stable against PMP, 2,6-di-*tert*-butylpyridine (TBP), or PMP hydrotriflate, while it decomposed in the presence of

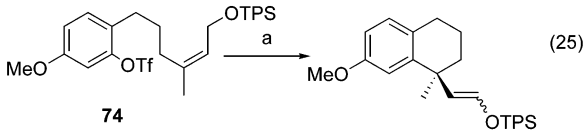
Scheme 3. Postulated Mechanism for the Formation of 67 and 68



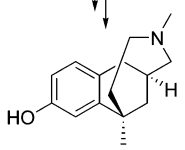
TBP hydrotriflate to give the β-hydride elimination Heck product **68** in 48% yield (er = 95:5) via the intermediate Pd−BINAP complex **72**. Thus, replacing PMP with TBP has been found to have a profound effect on the product distribution in this reaction.

On the basis of the above observations, these workers have suggested a possible mechanistic pathway for the formation of the various products from **66** or **69** which is governed by the acidity of the conjugate acid of the scavenger employed for trifluoromethanesulfonic acid (Scheme 3). Thus, in the presence of the stronger base PMP, palladacycles **70** and **73** are generated from **69** and **66**, respectively. The palladacycles **70** and **73** do not undergo β-hydride elimination, despite having three and two β-hydrogen atoms, respectively, since a tightly bound ligand (BINAP or the conjugate base of the protected isatin) would have to dissociate to generate a vacant coordination site. Therefore, palladacycle **70** is stable, while **73** undergoes β-methoxide elimination to generate **68**. In contrast, when the Heck reaction is carried out in the presence of the weaker base TBP, the corresponding TBP hydrotriflate, being a stronger acid, shifts the equilibrium from the palladacycle intermediates toward the cationic palladium(II) species **71** and **72**, which undergo facile β-hydride elimination to generate the conventional Heck products **67** and **68** (eq 24a). The palladacycle intermediate **70** is a rare example of a σ-alkylpalladium complex with β-hydrogen atoms present on a freely rotating β-carbon.

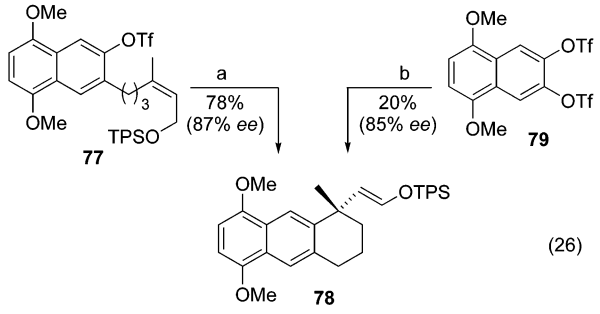
Shibasaki and co-workers have also reported the construction of a benzylic quaternary center by an enantioselective Heck reaction in the synthesis of (−)-eptazocine **76**[47] and halenaquinol **80**.[48] Thus, the cyclization of the (*Z*)-trisubstituted alkene **74** in the presence of a Pd−(*R*)-BINAP gave the tetrahydronaphthalene **75** in 90% ee (eq 25), whereas the opposite enantiomer of **75** was obtained with (*E*)-alkene **74**. The product **75** was subsequently utilized in the synthesis of the alkaloid **76**.

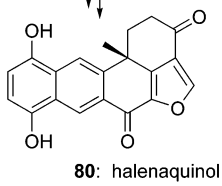


a) $Pd(OAc)_2$ (7 mol%), (*R*)-BINAP (17 mol%), K_2CO_3, THF, 60 °C, 72 h



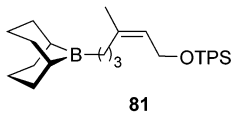
76: (–)-eptazocine





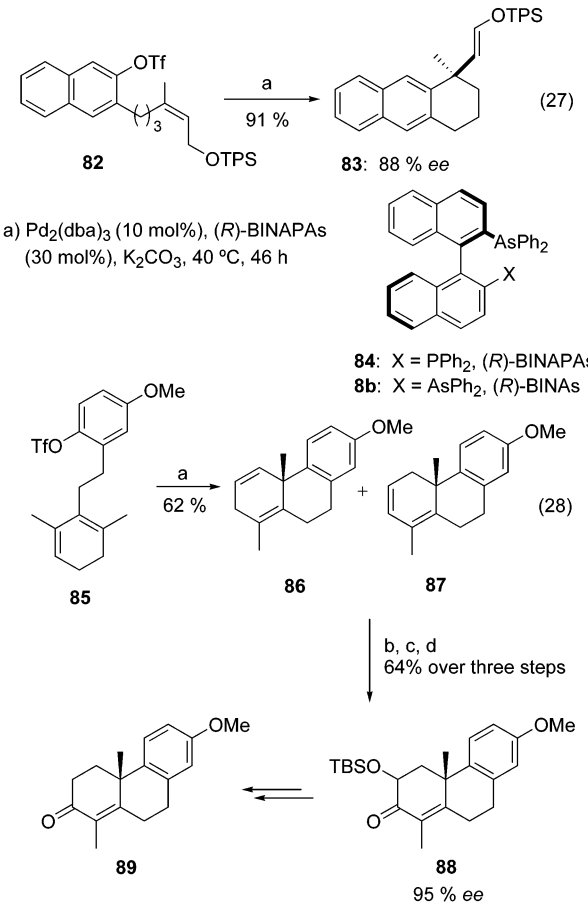
80: halenaquinol

a) $Pd(OAc)_2$ (10 mol%), (*S*)-BINAP (20 mol%), K_2CO_3, THF, 60 °C
b) **81**, $Pd(OAc)_2$ (20 mol%), (*S*)-BINAP (40 mol%), K_2CO_3, THF, 60 °C

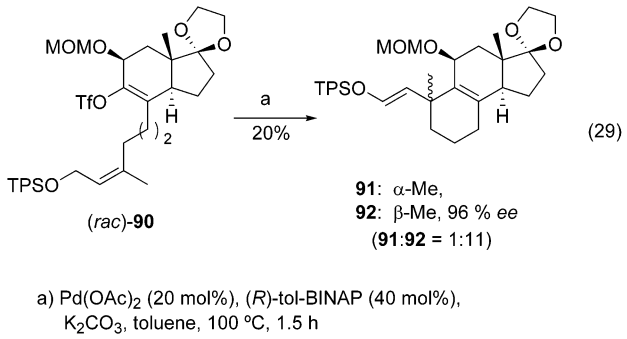


81

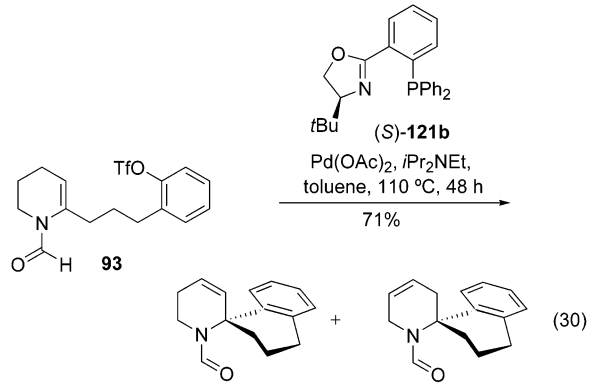
Similarly, the tetrahydroanthracene derivative **78**, a key intermediate in the enantioselective synthesis of halenaquinol **80**, was obtained in 78% yield and 87% ee via cyclization of the asymmetric Heck substrate **77** under similar conditions (eq 26).[48] The product **78** could also be obtained directly in high ee (85%), although in low yield (20%), in a one-pot Suzuki-type coupling of the C_2-symmetric triflate **79** with trialkylborane **81** and intramolecular enantioselective Heck reaction of the resulting intermediate.[49] In a comparative study related to the effectiveness of generating a benzylic quaternary center from the trialkyl-substituted alkene **82**, Shibasaki and coworkers synthesized the new chiral ligand BINAPAs (**84**) and found it to be superior to (*R*)-BINAP (**8a**) and also (*R*)-BINAs (**8b**) in this enantioselective Heck reaction (eq 27).[49]

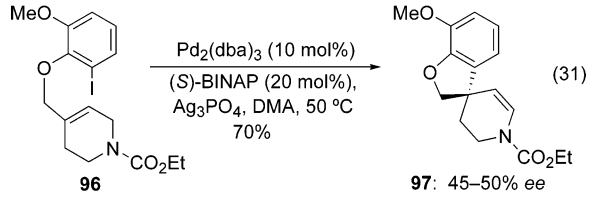


The same workers have also transformed the aryl triflate **85** into the bicyclic products **86** and **87** (3:1) with high enantiomeric excess (95%) and with complete selectivity toward 6-exo-cyclization (eq 28). The products **86** and **87** were converted into the enone **89**, which is a key intermediate in the synthesis of kaurene and abietic acid.[50,51] An efficient synthesis of the tetracyclic derivative **92**, a potential synthetic intermediate for the antifungal antibiotic wortmannin, has been recently reported[52] in extremely high optical purity (96%) by the same group, involving an asymmetric Heck cyclization and kinetic resolution of the racemic hydrindan **90** (eq 29).



Ripa and Hallberg[53] have reported the Pd-catalyzed intramolecular asymmetric Heck cyclization of the tetrahydropyridine derivative **93** in the presence of (*R*)-BINAP as chiral ligand to give isomeric mixtures of spirocyclic pyridines in low yields with rather long reaction times. However, with diphenylphosphinooxazoline **121b** as the chiral ligand, the spiropyridines **94** and **95** were obtained in good yields and with high enantioselectivities (eq 30), which constitutes the only example of the use of phosphinooxazoline[18] chiral ligands in an intramolecular asymmetric Heck reaction.

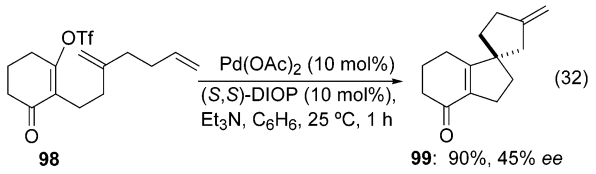


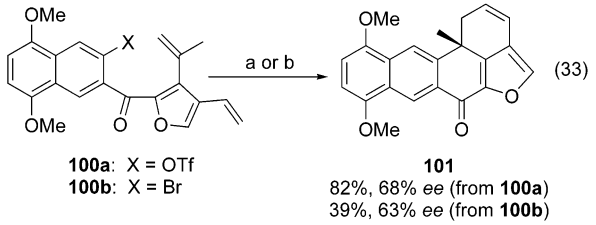


Another example of the asymmetric construction of a spirodihydropyridine framework by an enantioselective Heck reaction has been described by Cheng and co-workers.[54] Thus, the cyclization of the tetrahydropyridine derivative **98** with $Pd_2(dba)_3$−(*S*)-BINAP catalyst yielded the tricyclic fragment **97** of morphane in 70% yield, but with low ee (45−50%) (eq 31).

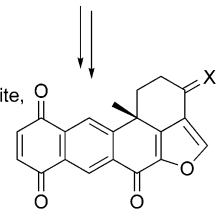
The possibility of extending the scope of intramolecular enantioselective Heck reactions for inclusion in Pd-mediated domino polyene cyclization[55] was earlier demonstrated by Overman in his first report[20] on the generation of a quaternary chiral center from

the triene **98** to give the spirocycle **99** in high yield with moderate enantioseectivity (eq 32).





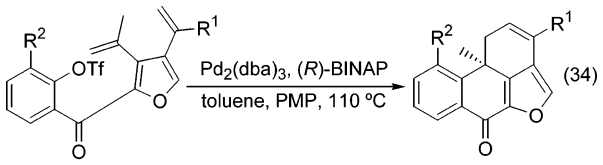
a) $Pd_2(dba)_3$ (2.5 mol%), (*S*)-BINAP (10 mol%), PMP, toluene, 110 °C, 10 h (for **100a**)
b) $Pd_2(dba)_3$ (5 mol%), (*S*)-BINAP (15 mol%), $CaCO_3$, Ag-exchanged zeolite, NMP, 80 °C, 4 d, (for **100b**)



102: X = H, (+)-xestoquinone
103: X = O, (+)-halenaquinone

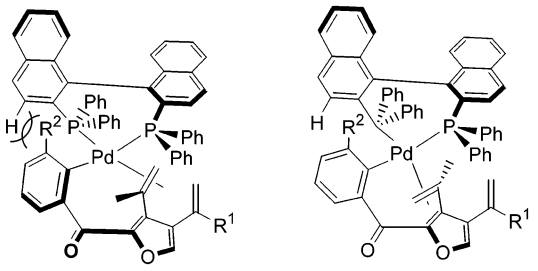
Keay and co-workers have recently reported[56a] the asymmetric synthesis of xestoquinone **102** from the pentacyclic intermediate **101**, which was obtained in 82% yield with 68% ee via one-pot cyclization of the triflate **100a** under enantioselective Heck reaction conditions, thus demonstrating the feasibility of a domino asymmetric Heck cyclization (eq 33). Shibasaki and co-workers have reported the transformation of the corresponding bromide **100b** to the product **103** in comparable ee but lower yield using silver zeolite.[56b] In a recent study[56c] on the model system **104** for the synthesis of halenaquinone **103**, Keay and co-workers observed a remote substituent effect on the enantioselectivity in intramolecular Heck reactions and reported the formation of the tetracyclic product **105** from **104** with surprisingly high ee (90%), in comparison to the corresponding unsubstituted derivative **107** formed from **106** in only 71% ee (eq 34).

These workers have carried out a series of PM3(tm) semi-empirical calculations on the unsaturated Pd complexes (*pro-R*)-**114** and (*pro-S*)-**114** to investigate the effect of the remote alkyl group[56d] on the ee's of the products in this cyclization. On the basis of these calculations, it has been shown that the energy difference between the two C-3 rotamers (*pro-R*)-**114** and (*pro-S*)-**114** increased when R^1 = H (R^2 = H) was changed to R^1 = Me (R^2 = H) when (*R*)-BINAP was modeled. It has been suggested that as the size of the R^1 group increased, the hydrogen atom (R^2) ortho to the palladium atom moved closer to the C-3′ hydrogen of (*R*)-BINAP in (*pro-R*)-**114**, while in the corresponding (*pro-S*)-**114** no such steric interaction was observed. This steric hindrance between the two hydrogens (C-3′ H and R^2 = H) appeared to be



104: R^1 = Me, R^2 = H
106: R^1 = R^2 = H
108: R^1 = H, R^2 = Me
110: R^1 = R^2 = Me
112: R^1 = Ph, R^2 = H

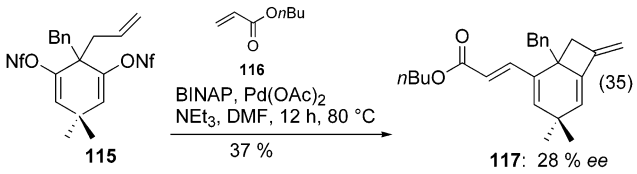
105: 78%, 90% *ee* (*R*)
107: 83%, 71% *ee* (*R*)
109: 71%, 96% *ee* (*R*)
111: 68%, 71% *ee* (*R*)
113 not formed



pro-*R*-**114** pro-*S*-**114**

responsible for the energy difference between (*pro-R*)-**114** and (*pro-S*)-**114** as the size of R^1 increased. This rationalization is further supported by placement of a bulkier methyl group ortho to the triflate (R^2 = Me) in the substrate **108**, which gave the product **109** with the highest ee of 96% due to a further increase of the steric interaction between C-3′ H and the R^2 (Me) group. On the other hand, the steric interaction between the two larger groups in the substrate **110** (R^1 = R^2 = Me) appears to be counterproductive, resulting in a drop of the ee (71%).

Bräse has reported the palladium-catalyzed enantioselective desymmetrization of bisnonaflate **115** on reaction with acrylate **116** in the presence of BINAP and palladium catalyst to give the bicyclic tetraene **117** with a quaternary carbon center in 37% yield and up to 28% ee (eq 35).[58]



2.2. Intermolecular Heck Reactions

The asymmetric *intra*molecular Heck reaction has been developed to the extent that it has been applied in the synthesis of a wide range of complex natural products. On the other hand, the asymmetric *inter*molecular Heck reaction has only been applied to test substrates as a means of developing this asymmetric methodology, and the related studies are limited mainly to five- and six-membered dihydroheterocycles, with 2,3-dihydrofuran becoming the standard substrate to test new chiral ligands for palladium-catalyzed intermolecular asymmetric Heck reaction.

2.2.1. 2,3-Dihydrofurans and Cyclic Enol Ethers

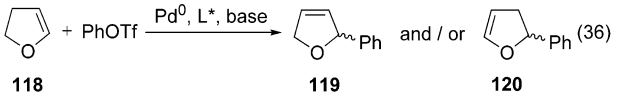
Hayashi and co-workers[59] were the first to study the asymmetric intermolecular Heck reaction em-

Table 3. Pd-Catalyzed Enantioselective Intermolecular Arylation of 2,3-Dihydrofuran (Eq 36)

			119		**120**		
entry	ligand	reaction conditions	yield (%)	ee (%)	yield (%)	ee (%)	ref
1	(*R*)-BINAP (**8a**)	$Pd(OAc)_2$, (*R*)-BINAP (**8a**), iPr_2NEt, C_6H_6, 30 °C, 66 h	11	67 (*S*)	89	93 (*R*)	59a
2	(*R*)-BINAP (**8a**)	$Pd(OAc)_2$, (*R*)-BINAP (**8a**), Proton Sponge, C_6H_6, 40 °C, 9 d	29	17 (*S*)	71	>96 (*R*)	59c
3	**121b**	$Pd_2(dba)_3$ (3 mol %), **121b** (6 mol %), iPr_2NEt, THF, 70 °C, 4 d	87	97			60
4	(*S*)-**131**	$Pd(OAc)_2$ (3 mol %), (*S*)-**131** (6 mol %), iPr_2NEt, C_6H_6, 40 °C, 7 d	3	98 (*R*)	65	98 (*S*)	61
5	(*R*)-BINAPAs (**84**)	$Pd(OAc)_2$ (5 mol %), **84** (10 mol %), iPr_2NEt, C_6H_6, 40 °C, 36 h	48	45 (*R*)	29	82 (*R*)	49
6	(*R*)-BITIANP (**31**)	$Pd_2(dba)_3$·dba (3 mol %), **31** (12 mol %), Proton Sponge, DMF, 90 °C, 18 h			84	91	62
7	(*R*)-BITIANP (**31**)	$Pd_2(dba)_3$·dba (3 mol %), **31** (12 mol %), iPr_2NEt, DMF, 90 °C, 20 h			90	90	62
8	(*R*)-**132**	$Pd(OAc)_2$ (3 mol %), (*R*)-**132**, iPr_2NEt, dioxane, 30 °C, 9 d	9	57	61	>97	63
9	(*S*)-**123a**	$Pd(dba)_2$ (3 mol %), (*S*)-**123a**, 60 °C, iPr_2NEt, THF, 8 h	80	76.5 (*R*)			64
10	(S,S_P)-**123b**	$Pd(dba)_2$ (3 mol %), (S,S_p)-**123b**, 60 °C, iPr_2NEt, THF, 8 h	72	83.5 (*S*)			64
11	(S,S_P)-**123c**	$Pd(dba)_2$ (3 mol %), (S,S_p)-**123c**, 60 °C, iPr_2NEt, THF, 8 h	79	88.5 (*R*)			64
12	(S,R_P)-**123d**	$Pd(dba)_2$ (3 mol %), (S,R_p)-**123d**, 60 °C, iPr_2NEt, THF, 8 h	75	92.1 (*R*)			64
13	(*S,S*)-**122**	$Pd_2(dba)_3$·dba (3 mol %), (*S,S*)-**122** (3 mol %), iPr_2NEt, THF, 70 °C, 18 h	85 65	81 (*R*) 88 (*R*)[a]			65
14	(*S,R*)-**122**	$Pd_2(dba)_3$·dba (3 mol %), (*S,R*)-**122** (3 mol %), iPr_2NEt, THF, 70 °C, 3 h	85 84	74 (*S*) 80 (*S*)[b]			65
15	**125c**	$Pd(dba)_2$ (5 mol %), **125c** (5.6 mol %), iPr_2NEt, THF, 65 °C, 3 d	100	93 (*R*)			66
16	**125b**	$Pd(dba)_2$ (5 mol %), **125b** (5.6 mol %), iPr_2NEt, THF, 65 °C, 1 d	100	96			66
17	**126b**	$Pd_2(dba)_3$ (1.5 mol %), **126b** (3 mol %), iPr_2NEt, C_6H_6, 75 °C, 3 d	95	82			67
18	**134a**	[$Pd(dba)_2$] (3 mol %), **134a** (6 mol %), Proton Sponge, 60 °C, 3 d	97	87	3[c]		18a
19	**134b**	[$Pd(dba)_2$] (3 mol %), **134b** (6 mol %), iPr_2NEt, 60 °C, 3 d	98	92	2[d]		18a
20	**135a**	[$Pd(dba)_2$] (3 mol %), **135a** (6 mol %), iPr_2NEt, 50 °C, 2 d	83	97	17[e]		18a
21	**135b**	[$Pd(dba)_2$] (3 mol %), **135b** (6 mol %), Proton Sponge, 50 °C, 2 d	95	99	5[f]		18a
22	(−)-**136**	[$Pd(dba)_2$], (−)-**136** iPr_2NEt, THF, 70 °C, 2 d	68	88	84	91	72
23	(*S*)-**133**	$Pd(OAc)_2$ (5 mol %), (*S*)-**133** (10 mol %), Na_2CO_3, C_6H_6, 60 °C			74	60	73
24	**129**	$Pd_2(dba)_3$·dba (4 mol %), **129** (15 mol %), iPr_2NEt, C_6H_6, 70 °C, 5 d	81	96 (*R*)			69
25	**130**	$Pd_2(dba)_3$·dba (1.5 mol %), (*R*)-**130** (5 mol %), iPr_2NEt, THF, 70 °C, 4 d	79	91 (*S*)			71
26	**128**	$Pd_2(dba)_3$ (2.5 mol %), **128** (6 mol %), iPr_2NEt, C_6H_6, 70 °C, 22 h	100	96 (*R*)			68
27	**124b**	$Pd(dba)_2$·**124b** (3 mol %), Proton Sponge, toluene, 110 °C, 14 h	61	98 (*R*)			70

[a] 30 °C, 240 h. [b] 30 °C, 168 h. [c] 97% conversion. [d] 83% conversion. [e] 100% conversion. [f] 48% conversion.

ploying 2,3-dihydrofuran (**118**), an aryl triflate, and the $Pd(OAc)_2$−(*R*)-BINAP catalyst system, resulting in the formation of (*R*)-2-aryl-2,3-dihydrofuran **120** as the major product, together with a minor amount of (*S*)-2,5-dihydrofuran **119** (eq 36) (Table 3, entry 1). The best compromise between yield and ee's was



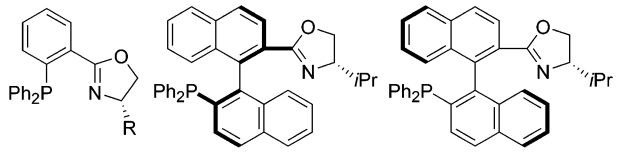
obtained when Proton Sponge was used as a base, yielding a mixture of the furans **119** and **120** in a 29:71 ratio, with the latter being formed in greater than 96% ee.[59b,c] The detailed mechanism for the preferential formation of the thermodynamically more stable regioisomer **120** has been discussed in earlier reviews.[17,18] The double bond migration step was found to involve kinetic resolution; therefore, the major product, i.e., (*R*)-2-phenyl-2,3-dihydrofuran **120**, was obtained with high ee, even though the initial insertion of the double bond into the Pd−aryl bond proceeded with only moderate enantioselectivity. The extent of the double bond migration, and consequently the regioselectivity and enantioselectivity of the reaction, depends on the reaction condi-

tions, particularly on the nature of the base. In a dramatic extension to this work, Pfaltz and co-workers[18,60] have described the application of diphenylphosphinooxazoline ligands **121** for the arylation and alkenylation of **118**, affording both the best enantioselectivities and the highest catalytic activity.[18] In contrast to the regioisomeric problem observed by Hayashi, the phenylation of dihydrofuran **118** in the presence of Pd−**121b** produced only (*R*)-**119** in 87% yield and 97% ee (Table 3, entry 3).

Unlike in the reactions with a Pd−BINAP catalyst, bases such as triethylamine or *N*,*N*-diisopropylamine proved to be equally or even slightly more effective. The substituent at the stereogenic center of the oxazoline ligand **121** has a distinct influence on the reactivity of the catalyst, and the best yields were obtained with **121b** (R = *t*Bu), whereas with phosphinooxazoline ligands containing less bulky groups at the stereogenic center (**121a**, **121c**, R = *i*Pr, Ph), the reaction is much slower, resulting in lower conversion.[18] These findings are rather unexpected because the steric hindrance near the metal center often slows a metal-catalyzed process. At this stage the authors have no obvious explanation for these observations. Pregosin and co-workers[61] have used (*S*)-MeO−BIPHEP **131** as a ligand for the asymmetric arylation of **118** to obtain products **119** and **120** in a 1:22 ratio. The reaction proceeds slowly but with an excellent enantioselectivity (Table 3, entry 4). Several new chiral ligands have been employed for the asymmetric arylation of the dihydrofuran **118** (Chart 1), and the results are summarized in Table 3.

Tietze and co-workers have recently reported[62] the use of the new ligands, (*R*)-BITIANP **31** and (+)-TMBTP **30**, in the asymmetric arylation of **118** with complete regioselectivity, high ee's, and good yields (Table 3, entries 6 and 7). (*R*)-BITIANP was found to be more effective, yielding **120** in 84% yield and 91% ee within 18 h, which is noteworthy since the other chiral ligands, such as **121b**, require 3−5 days for this reaction. Other substituted phenyl triflates containing either electron-donating or electron-withdrawing groups were also reacted with **118** under identical conditions to give products **120** with high regio- and enantioselectivity (92−96%). Keay and co-workers have recently reported the synthesis and reactivity of the novel chiral ligand BINAPFu **132** in the asymmetric arylation of **118**, yielding mainly the 2,3-dihydrofuran **120** in 61% yield and 97% ee (Table 3, entry 8).[63] In a recent paper, Hou and co-workers[64] have described the use of planar chiral 1,1′-*P*,*N*-ferrocene derivatives **123** for the asymmetric arylation of **118** and demonstrated that the planar chirality is decisive in exerting control over both the absolute configuration and the enantiomeric excess of the product **119**, which could be controlled by changing the size of the planar group in **123** and/or the configuration of the planar chirality. The corresponding 2,5-dihydrofuran **119** was formed as the sole product with these ligands (Table 3, entries 9−12). The use of ligand **123a** under optimized conditions gave (*R*)-**119** in 80% yield with 76.5% ee (Table 3, entry 9). On the other hand, a

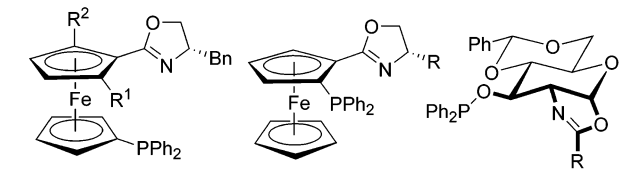
Chart 1



121a: R = *i*Pr
121b: R = *t*Bu
121c: R = Ph
121d: R = Bn

(*S*,*S*)-**122**

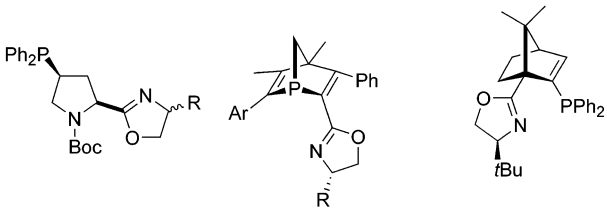
(*S*,*R*)-**122**



(*S*)-**123a**: R^1= R^2= H
(*S*,S_p)-**123b**: R^1= TMS, R^2= H
(*S*,S_p)-**123c**: R^1= H, R^2= Me
(*S*,R_p)-**123d**: R^1= H, R^2= TMS

124a: R = *i*Pr
124b: R = *t*Bu

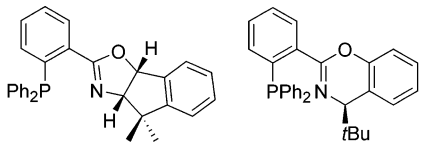
125a: R = *t*Bu
125b: R = Bn
125c: R = *i*Bu



126a: α-*i*Pr
126b: β-*i*Pr

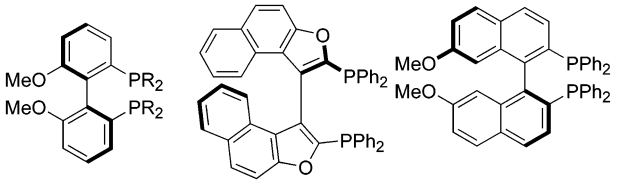
127a: Ar = Ph, R = α-*t*Bu
127b: Ar = anthracyl, R = α-*i*Pr

128



129

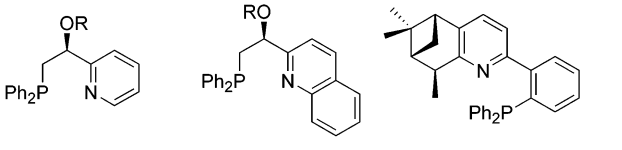
(*R*)-**130**



131: R = 3,5-(*t*Bu)$_2$C$_6$H$_3$ (*S*)-MeO-BIPHEP

132: (*R*)-BINAPFu

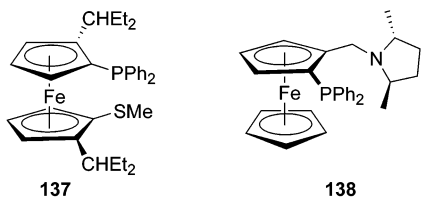
133



134a: R = TIPS
134b: R = TPS

135a: R = TIPS
135b: R = TPS

(–)-**136**: *iso*-PINPHOS



137

138

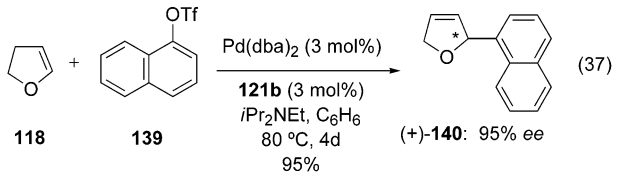
dramatic change in the enantioselectivity of the reaction was observed with (S,S_p)-**123b**, containing an (S_p)-TMS planar chiral group. The enantiomeric excess of the 3,5-dihydrofuran **119** changed from 76.5% with (*R*)-configuration (by using ligand **123a**) to 83.5% with (*S*)-configuration (entry 10). On the other hand, **123c**, containing an (S_p)-Me planar chiral group, provided a remarkable improvement in the ee value (88.5%, (*R*)-configuration, entry 11). Augmenting the steric bulk of the newly introduced planar chiral group in (S,R_p)-**123d** from Me to Me_3Si increased the ee value of (*R*)-**119** to 92% (entry 12). It is suggested that the planar chirality in **123b**−**d** controls and tunes the ee values and the absolute configuration of the product **119** by changing the ratio of rotamers of the axial chirality on coordinating with Pd metal due to its steric repulsion of the coordinating center.

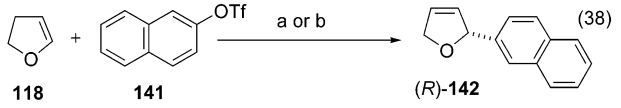
Hayashi and co-workers[65] recently reported the synthesis of novel palladium complexes coordinated with (*S*,*S*)- and (*S*,*R*)-2-[4-(isopropyl)oxazol-2-yl)]-2′-diphenylphosphino-1,1′-binaphthyls **122** and applied them for asymmetric arylation of **118**, with the highest ee of 88% (Table 3, entry 13) for product **119**. The ligands **122**, with opposite configuration with respect to their axial chirality on the binaphthyl backbone, induce opposite configurations in the product **119** respectively (entries 13 and 14). These studies demonstrate that the axial chirality in the ligands **122** more strongly regulates the chiral environment around the palladium center and has a greater influence on the stereochemical outcome than the central chirality in the corresponding oxazoline unit.

Chiral phosphinite oxazolines **125**, derived from D-glucosamine hydrochloride, are also shown to be highly effective ligands, as reported by Uemura and co-workers.[66] Thus, the asymmetric arylation of **118** provided **119** in quantitative yield and up to 93−96% ee (Table 3, entries 15 and 16). Recently, proline-derived phosphinooxazoline **126b**,[67] bicyclic phosphinooxazoline **128**,[68] indano-fused **129**,[69] ferrocenyl phosphinooxazolines **124b**,[70] the corresponding benzoxazine **130**,[71] and pyridine (or quinoline)-based diphenylphosphines **134a**,**b**, **135a**,**b**,[18a] **136**,[72] and 7,7′-bismethoxy-(*S*)-BINAP **133**[73] chiral ligands have been successfully investigated in asymmetric phenylation of dihydrofuran **118**, yielding mainly 2,5-dihydrofuran **119** with high regio- and enantioselectivity (Chart 1, Table 3, entries 17−27).

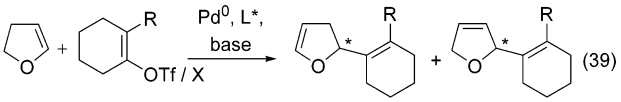
Most of the studies on arylation involve phenyl triflate for the arylation of **118** with Pd complexes of various ligands. In an isolated example, Pfaltz and co-workers have reacted 1-naphthyl triflate with 2,3-dihydrofuran under enantioselective Heck reaction conditions using **121b** as the chiral ligand to afford 1-(1′-naphthyl)-2,5-dihydrofuran **140** in 95% yield and 95% ee (eq 37).[18,60]

Recently, Kang and co-workers have reported intermolecular Heck reaction of dihydrofuran **118** with 2-naphthyl triflate in the presence of a new *P*,*S*-hybrid ferrocenyl chiral ligand **137** to give 2,5-dihydrofuran **142** as the major isomer in 64% yield but in moderate ee (40%) (eq 38).[74] High enantioselection has also been observed in the alkenylation of 2,3-dihydrofuran **118** with the cyclohexenyl triflates **143** and **144** in the presence of various chiral ligands (eq 39) (Table 4), which has been investigated in detail by Pfaltz and co-workers[18a,60] using chiral phosphinooxazoline ligands.





a) $Pd(OAc)_2$ (0.2 mol%), (*R*)-BINAP (0.38 mmol), proton sponge, C_6H_6, 40 ºC, 2 d, 52%, >96% *ee*
b) $Pd(dba)_2$ (3 mol%), **137** (6 mol%), Et_3N, C_6H_6, 70 ºC, 22 h, 64%, 40% *ee*



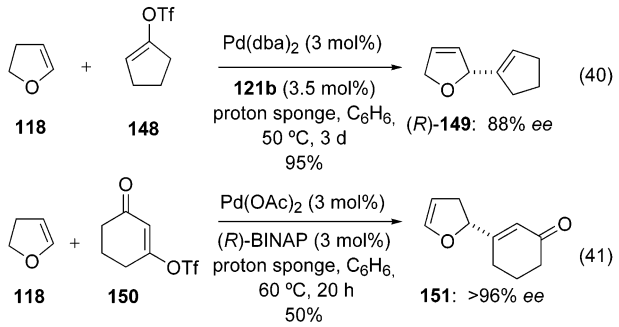
With (*R*)-BINAP as the ligand, the isomeric 2-cyclohexenyl-2,3-dihydrofuran **145** was obtained in moderate yield with 87% ee (entry 1),[75] whereas remarkable increases in both yield and enantioselectivity were observed in the enantioselective Heck reaction between **118** and 2-ethoxycarbonyl-cyclohexenyl triflate **144** to afford the corresponding 2,3-dihydrofuran **146** in 96% ee (Table 4, entry 2).[75] However, the phosphinooxazoline **121b** was found to be the best ligand for this reaction, giving 2,5-dihydrofuran **147** as the only regioisomer in 92% yield and >99% ee (Table 4, entry 3),[18a] which is a major improvement compared to the ee's obtained with the BINAP ligand. Another chiral ligand used in the cycloalkenylation of **118** is (*R*)-BITIANP (Tietze et al.[62]), which also gave only the 2,3-dihydrofuran **145** in good yield and high ee (Table 4, entry 4). On the other hand, the alkenylation of **118** with **143** in the presence of the novel proline-derived phosphine-oxazolines **126a** and **126b** or the bicyclic *P*,*N*-ligands **127a**,**b**[76] and **128**,[68] reported recently by Gilbertson, yielded only the 2,5-dihydrofuran **147** with reasonably high ee's (Table 4, entries 5−7 and 11). Shibasaki and co-workers have reported the alkenylation of **118** with the cyclohexenyl iodinium salt in the presence of (*R*)-BINAP to furnish 2,5-dihydrofuran **147** as the only regioisomer with 78% ee, although in low yield (entry 8).[77] The other chiral ligands employed in enantioselective Heck reactions of **118** with cyclohexenyl triflate are indano-fused diphenylphosphinooxazoline **129**,[69] phosphinophenylbenzoxazine **130**,[71] and phosphinophenyl ferrocenyloxazoline **124b**[70] (entries 9, 10, and 12, Table 2), yielding mainly 2,5-dihydrofuran **147** with high ee's,

Table 4. Pd-Catalyzed Enantioselective Intermolecular Cyclohexenylation of 2,3-Dihydrofuran 118 (Eq 39)

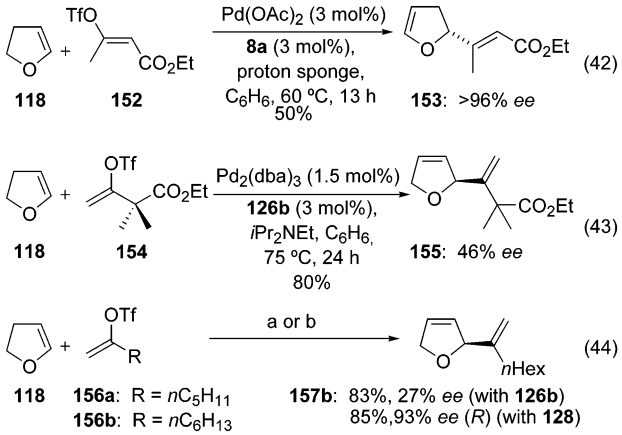
				145/146		147		
entry	R^1	ligand	reaction conditions	yield (%)	ee (%)	yield (%)	ee (%)	ref
1	H	(*R*)-BINAP (**8a**)	$Pd(OAc)_2$ (3 mol %), **8a** (3 mol %), Proton Sponge, C_6H_6, 30 °C, 91 h	58	87 (*R*)			75
2	CO_2Et	(*R*)-BINAP (**8a**)	$Pd(OAc)_2$ (3 mol %), **8a** (3 mol %), Proton Sponge,C_6H_6, 50 °C, 56 h	62	>96 (*R*)			75
3	H	**121b**	[$Pd_2(dba)_3$] (3 mol %), **121b** (6 mol %), iPr_2NEt, C_6H_6, 30 °C, 3 d			92	99 (*R*)	18a, 60
4	H	(*R*)-BITIANP (**31**)	$Pd_2(dba)_3$·dba (3 mol %), **31** (12 mol %), Proton Sponge, DMF, 90 °C, 13 h	76	86 (*R*)			62
5	H	**126a** or **126b**	Pd_2dba_3 (3 mol %), **126** (3 mol %), dioxan, 36 h, iPr_2NEt or Et_3N			99 99	80 (*S*) 86[a] (*R*)	67 67
6	H	**127a**	$Pd_2(dba)_3$ (3 mol %), **127a** (8.5 mol %), iPr_2NEt, THF, rt, 80 h			91	93 (*R*)	76
7	H	**127b**	$Pd_2(dba)_3$ (3 mol %), **127b** (8.5 mol %), iPr_2NEt, THF, C_6H_6, rt, 20 h			94	56 (*R*)	76
8	H (X = I)	(*R*)-BINAP (**8a**)	$Pd(OAc)_2$ (40 mol %), **8a** (60 mol %), Proton Sponge, CH_2Cl_2, 25 °C, 20 h			22	78	77
9	H	**129**	$Pd_2(dba)_3$ (4 mol %), **129** (15 mol %), iPr_2NEt, C_6H_6, 70 °C, 5 d			91	98 (*R*)	69
10	H	(*R*)-**130**	$Pd_2(dba)_3$ (1.5 mol %), (*R*)-**130** (5 mol %), iPr_2NEt, C_6H_6, rt, 3 d			55	94 (*S*)	71
11	H	**128**	$Pd_2(dba)_3$ (2.5 mol %), **128** (6 mol %), iPr_2NEt, C_6H_6, 70 °C, 22 h			100	94 (*R*)	68
12	H	**124b**	$Pd_2(dba)_3$·**124b** (3 mol %), Proton Sponge, toluene, 110 °C, 14 d			75	85 (*R*)	70

[a] With Et_3N.

whereas the ferrocenyl ligand **138** explored recently by Guiry and co-workers[70] gave low ee's in both phenylation and cyclohexenylation of **118**. The alkenylation of **118** with cyclopentenyl triflate in the presence of the diphenylphosphinooxazoline ligand **121b** also provides 2-cyclopentenyl-2,5-dihydrofuran **149** in high yields and ee's (eq 40).[18,60] Hayashi and co-workers[75] have also used cyclohexenone-3-triflate **150** as an alkenylating agent in the presence of (*R*)-BINAP to afford only the 2,3-dihydrofuran derivative **151** in remarkably high enantioselectivity (eq 41).



Interestingly, the reaction of **118** with acyclic alkenyl triflate **152**, bearing an electron-withdrawing group, in the presence of Pd−(*R*)-BINAP proceeded rapidly (13 h) with high enantioselectivity up to >96% (eq 42).[75] On the other hand, the corresponding 1-pentylethenyl triflate **156a** did not react under these conditions. Recently, Gilbertson examined the alkenylation of **118** with the acyclic triflates **154** and **156b** in the presence of novel proline-derived phosphinooxazoline ligands **126b**[67] and the bicyclic *P*,*N*-ligand **128**[68] (eqs 43 and 44).The product 2,5-dihydrofurans **155** and **157b** were formed in high yields but with moderate ee's with **126b**, whereas the

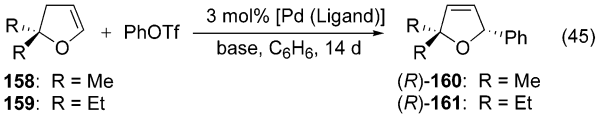


a) $Pd_2(dba)_3$ (1.5 mol%), **126b** (3 mol%), iPr_2NEt, C_6H_6, 75 °C, 24 h

b) $Pd_2(dba)_3$ (2.5 mol%), **128** (6 mol%), iPr_2NEt, C_6H_6, 95 °C, 36 h

ligand **128** was found to be highly efficient in this reaction, yielding dihydrofuran **157b** in 85% yield and 93% ee.[68]

Guiry and co-workers have recently reported 2,2-dimethyl- and 2,2-diethyl-2,3-dihydrofurans **158** and **159** as new test substrates for the intermolecular asymmetric Heck reaction that allow easy and direct comparison of a wide range of ligands in terms of reactivity and enantioselectivity, due to the fact that only one regioisomer can be formed (eqs 45 and 46).[78−79] Thus, in the phenylation of 2,2-dimethyl-

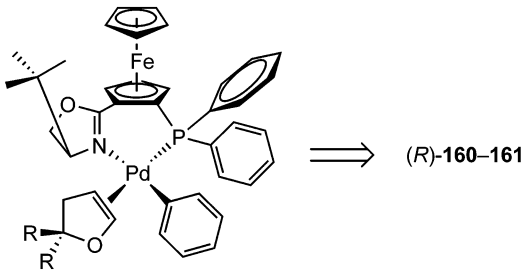


furan **158**[78a] in the presence of Pd complexes of either

Table 5. Enantioselective Intermolecular Heck Arylation of 2,2-Dialkylfurans 158 and 159 (Eq 45)

entry	substrate	L*	base	temp (°C)	product	yield (%)	ee (%)
1	**158**	**8a**[a]	*i*Pr$_2$NEt	40	**160**	100	76 (*R*)
2	**158**	**121b**[b]	Proton Sponge	80	**160**	100	92 (*R*)
3	**158**	**124b**[b]	Et$_3$N	80	**160**	90	98 (*R*)
4	**158**	**124b**[b]	Proton Sponge	80	**160**	27	95 (*R*)
5	**158**	**124b**[b]	*i*Pr$_2$NEt	80	**160**	68	98 (*R*)
6	**159**	**8a**[a]	*i*Pr$_2$NEt	40	**161**	47	54 (*R*)
7	**159**	**121b**[b]	Proton Sponge	80	**161**	74	94 (*R*)
8	**159**	**124b**[b]	Proton Sponge	80	**161**	17	43 (*R*)

[a] Catalyst generated from Pd(OAc)$_2$. [b] From Pd$_2$(dba)$_3$, C$_6$H$_6$, 14 d.



162

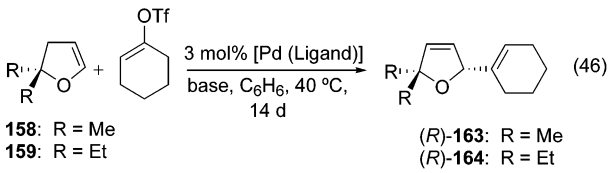
Table 6. Enantioselective Intermolecular Alkenylation of 2,2-Dialkyl-2,3-dihydrofurans 158 and 159 (Eq 46)

entry	substrate	L*	base	product	yield (%)	ee (%)
1	**158**	**8a**[a]	*i*Pr$_2$NEt	**163**	44	37
2	**158**	**121b**[b]	Proton Sponge	**163**	68	97
3	**158**	**121b**[b]	*i*Pr$_2$NEt	**163**	60	40
4	**158**	**124b**[b]	*i*Pr$_2$NEt	**163**	73	87
5	**159**	**8a**[a]	*i*Pr$_2$NEt	**164**	34	39
6	**159**	**121b**[b]	Proton Sponge	**164**	24	93
7	**159**	**121b**[b]	*i*Pr$_2$NEt	**164**	34	82
8	**159**	**124b**[b]	Proton Sponge	**164**	16	25

[a] Catalyst generated from Pd(OAc)$_2$. [b] From Pd$_2$(dba)$_3$. [b] Reaction conditions: C$_6$H$_6$, 40 °C, 14 d.

(*R*)-BINAP, phosphinooxazolines **121a**−**d**, or the diphenylphosphinoferrocenyloxazolines **124a**,**b**, the product **160** could be obtained with a maximum ee of 98% in 90% chemical yield with the ligand **124b** (Table 5, entry 3) in the presence of Et$_3$N as base, which stands in contrast to Hayashi's work, where the use of Proton Sponge provided the highest ee (Table 3, entry 2) in comparison to Hünig's base and Et$_3$N.[59c]

The same catalyst systems were also compared in the asymmetric cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran (eq 46) (Table 6).[78b] The diphosphine

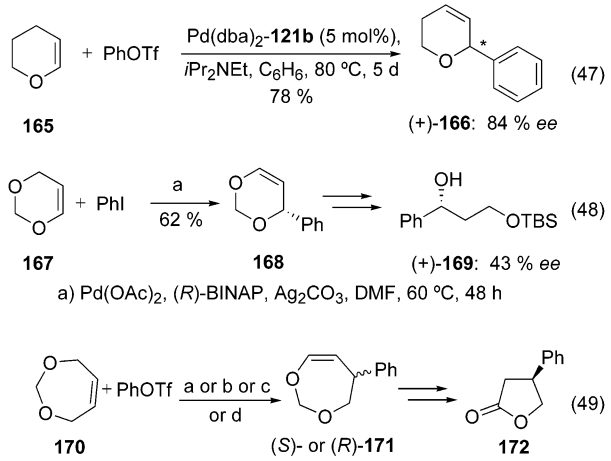


(*R*)-BINAP gave poor results (entry 1) in comparison to the use of 2,3-dihydrofuran **118** as the substrate.[75] With the phosphineamine ligands **121b** and **124b**, the highest enantioselectivity of 97% (68% yield Table 6, entry 2) was obtained using a catalyst derived from the *tert*-butyl-substituted diphenylphosphinoarylloxazoline ligand **121b**, with Proton Sponge as base. The results were better than those obtained using a trialkylamine (Table 6, entry 2 versus entry 3) In a recent paper,[79] the same workers extended these studies to 2,2-diethyl-2,3-dihydrofuran **159** (eqs 45 and 46) (Table 5, entries 6−8, and Table 6, entries 5−8) and observed lower chemical yields but similar enantioselectivities for the product dihydrofurans **161** and **164** in comparison to the corresponding 2,2-dimethyl analogue **158**. Thus, optimum ee's of 94 and 93% were obtained for the phenylation (Table 5, entry 7) and the cyclohexenylation (Table 6, entry 6) respectively with the *tert*-butyl-substituted diphenylphosphinooxazoline ligand **121b**. The decline in chemical yields of the products **161** and **164** from the diethyl-substituted substrate **159**, compared with those obtained using the dimethyl-substituted furan **158**, has been rationalized in terms of increased ligand−reactant steric interaction in the migratory insertion transition state caused by the bulkier alkene **159** (versus **158**). Similarly, a comparison of ee values for **161** and **164** obtained with three ligands versus those obtained for **160** and **163** revealed that the ee values decreased only slightly with complexes of (*R*)-BINAP (Table 5, entry 1 versus entry 6), remained reasonably constant for complexes of **121b** (Table 5, entry 2 versus entry 7), but surprisingly fell dramatically for the complexes of diphenylphosphinoferrocenyloxazoline **124b** (Table 5 versus entry 8, and Table 6, entry 4 versus entry 8). A transition-state intermediate **162** with alkene approaching trans to phosphorus has been proposed by these workers for the formation of (*R*)-products **160** and **161** in asymmetric phenylaton of **118** in the presence of *P*,*N*-ferrocene ligand **124b**.[70] This work again highlights the difficulty in finding a ligand suitable for a wide spectrum of substrates and need for fine-tuning the electronic and steric properties of the ligands for the individual substrates.

Table 7. Intermolecular Enantioselective Arylation of 2,3-Dihydropyrrole 173 (Eq 50)

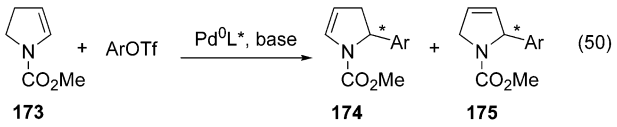
				174		175	
entry	Ar	L*	reaction conditions	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	(*R*)-BINAP (**8a**)	$Pd(OAc)_2$, **8a**	68	74	27	27
2	Ph	**121b**	$Pd_2(dba)_3$(3 mol %), **121b** (6 mol %), C_6H_6, iPr_2NEt, 80°C, 5 d		93 (*S*)	88	85
3	Ph	(*S*)-BINAP (*ent*-**8a**)	$Pd_2(dba)_3$ (3 mol %), *ent*-**8a** (12 mol %), Proton Sponge, DMF, 90 °C, 20−24 h	84			
4	4-CNC_6H_4	*ent*-**8a**	$Pd_2(dba)_3$ (3 mol %), *ent*-**8a** (12 mol %), Proton Sponge, DMF, 90 °C, 20−24 h	87	94 (*S*)		
5	4-AcC_6H_4	*ent*-**8a**	$Pd_2(dba)_3$ (3 mol %), *ent*-**8a** (12 mol %), Proton Sponge, DMF, 90 °C, 20−24 h	92	95 (*S*)		
6	Ph	(*R*)-TMBTP (*ent*-**30**)	$Pd_2(dba)_3$ (3 mol %), *ent*-**30** (12 mol %), Proton Sponge, DMF, 90 °C, 20−24 h	19	2 (*R*)	72	
7	4-CNC_6H_4	*ent*-**30**	$Pd_2(dba)_3$ (3 mol %), *ent*-**30** (12 mol %), Proton Sponge, DMF, 90 °C, 20−24 h	16	2 (*R*)	66	

Intermolecular asymmetric arylation has also been carried out on a few other oxygen heterocycles, such as tetrahydropyran **165** (eq 47), cyclic enol ether **167** (eq 48), and dihydrooxepin **170** (eq 49).[80] The dihydropyran **165** proved to be less reactive with phosphinooxazoline ligand **121b** in comparison to dihydrofuran **118**, but at somewhat higher temperature the 2-aryl derivative **166** was obtained in good yield with 84% ee.[18] The asymmetric arylation of **167** to give **168** in the presence of (*R*)-BINAP proceeds in only modest yield (62%) and ee (43%), and the product can be converted into the 1,3-diol **169** (43% ee), an intermediate in the Sharpless synthesis of (*R*)-fluoxetine.[81] Shibasaki and co-workers[82] have first reported the intermolecular enantioselective Heck reaction of the 4,7-dihydro-1,3-dioxepin system **170** using Pd^0−(*S*)-BINAP catalyst along with molecular sieves, enhancing both the chemical yield (84%) and ee (72%) of the product enol ether **171**, which was easily converted to the synthetically useful chiral *β*-aryl-*γ*-butyrolactone intermediates **172** (eq 49). Significantly improved ee's (up to 96%) for this process have been reported recently using the phosphinooxazoline ligands **121b**,[18a] **129**,[69] and **128**.[68]



2.2.2. Intermolecular Arylation and Alkenylation of Dihydropyrroles

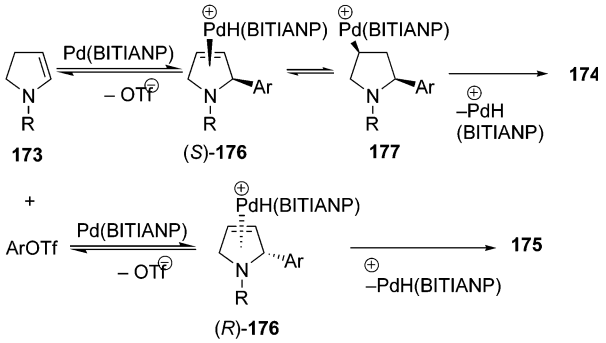
Asymmetric intermolecular arylation and alkenylation studies have also been reported on 2,3- and 2,5-dihydropyrroles **173** and **180** (eqs 50 and 51), displaying patterns of regio- and enantioselectivity similar to those observed for dihydrofuran **118**. Thus,



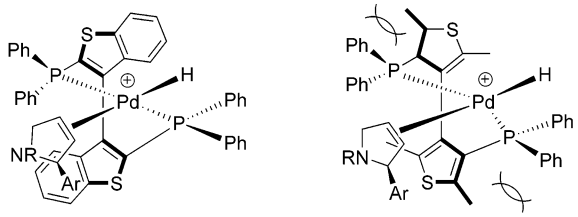
Hayashi and co-workers first examined[83] the arylation of 2,3-dihydropyrrole **173** with (*R*)-BINAP to give 2-phenyl-2,3-dihydropyrrole **174** as the main product (68%, 74% ee), along with 27% yield of the minor isomer **175** (Table 7, entry 1), whereas under Pfaltz reaction conditions with the phosphinooxazoline ligand **121b**, the 2,5-dihydropyrrole **175** was obtained as the sole product in high yield (88%, 85% ee, entry 2).

In a recent publication, Tietze and co-workers have reported[84] the asymmetric arylation and alkenylation of 2,3-dihydropyrrole **173** with the new chiral ligand (*S*)-BITIANP (*ent*-**31**), yielding 5-aryl-2-pyrrolines **174** in high yields and regioselectivity and with excellent enantioselectivity (93−95%, Table 7, entries 3−5). Unlike in the reaction with (*R*)-BINAP, the 3-pyrroline regioisomer **175** was formed in negligible yields. Also noteworthy are the shorter reaction time (20−24 h) and the high reaction temperature, which did not affect the enantioselectivity of the transformations. The use of the chiral ligand (*R*)-TMBTP **30** was less successful, yielding **174** and **175** with poor regioselectivity with a preferential formation of **175**, although without any enantioselectivity (Table 7, entries 6 and 7). The superiority of BITIANP **31** in comparison to BINAP and TMBTP in these reactions has been rationalized in terms of electronic and steric factors. Thus, the relatively high electron density at the phosphorus atoms in the electron-rich benzothiophene ring of **31** causes the phosphorus atoms to bind more strongly to the electron-deficient palladium and results in the enhancement of the oxidative addition of aryl triflates and overall high reaction rates. Therefore, the reaction with BITIANP **31** is highly selective within a shorter time even at higher temperatures, whereas the Pd complexes with ligands such as BINAP may partially dissociate at higher

Scheme 4. Probable Mechanism of the Intermolecular Enantioselective Arylation of 173



temperatures, resulting in diminished enantioselectivities. The authors have also suggested a probable mechanism for the preferential formation of the 2-pyrroline derivative **174** with only a negligible amount of the isomer **175** in the presence of the BITIANP ligand (Scheme 4). Thus, apparently, the product **174** is formed by elimination−reinsertion of a Pd−H species (**176** → **177** → **174**). However, unlike Hayashi's mechanism involving the kinetic resolution of (*R*)- and (*S*)-**176** for the observed enhanced facial selectivity, it is suggested that the first step (**173** → (*S*)-**176**) itself probably proceeds with high facial selectivity. Alternatively, the formation of (*R*)-**176** may be reversible, together with its relatively slow dissociation to **175**, compared to the reaction of (*S*)-**176** to give **174** via **177**, as shown in Scheme 4. Tietze and co-workers have further suggested transition-state models such as **178** and **179** to account for the

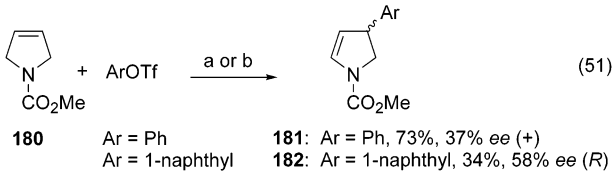


178 **179**

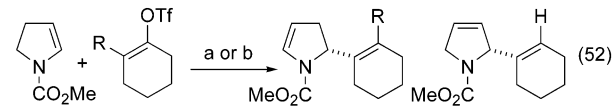
observed difference in reactivity with BITIANP **31** in comparison to either BINAP or TMBTP **30**. Thus, with the BITIANP ligand **31**, as a transition-state structure **178** with a wider coordination sphere due to the sterically less demanding benzothiophene moieties is formed, allowing the reinsertion of the Pd−H species to give **174** via the intermediate **177**. However, in the Pd complex **179** with TMBTP **30**, bearing four methyl groups, the coordination sphere is much smaller, thus making the reinsertion of the Pd−H species less possible, so that the 5-aryl-3-pyrrolines **175** are formed as the main products.

Pfaltz and co-workers have also reported the asymmetric arylation of 2,5-dihydropyrrole **180** with phenyl triflate in the presence of Pd−phosphinooxazoline **121b**, which gave the product 4-aryl-2-pyrroline **181** with a much lower enantioselectivity (37%) (eq 51).[18a]

The 2,5-dihydropyrrole **180** has also been arylated with 1-naphthyl triflate[85] to afford **182** in only moderate yield (34%) and ee (58%). The use of thallium triacetate as the cocatalyst in this reaction has been reported to suppress the formation of the



a) $Pd_2(dba)_3$ (3 mol%), **121b** (6 mol%), iPr_2NEt, C_6H_6, 80 °C, 5 d
b) $Pd(OAc)_2$, (*R*)-BINAP, TlOAc, iPr_2NEt, DMF, 60 °C, 16 h



a) $Pd(OAc)_2$ (3 mol%) (*R*)-BINAP (**8a**) (3 mol%), proton sponge, C_6H_6, **183**: 45%, 96% *ee* (*R*) after 14 d at 30 °C
184: 95%, >99% *ee* (*R*) after 20 d at 40 °C
b) $Pd(dba)_2$ (3 mol%), (*S*)-BITIANP (**31**) (12 mol%), proton sponge, DMF, 90 °C, 18 h, *ent*-**183**, 73%, 91% *ee* ; *ent*-**183**:**185** (4:1)

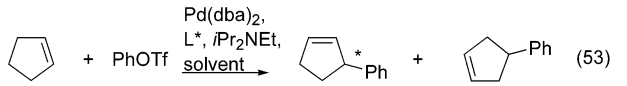
undesirable 2-arylation product (resulting by initial isomerization of the double bond in **180**).[85]

The enantioselective Heck reaction of 2,3-dihydropyrrole **173** has also been extended successfully to cycloalkenyl triflates **143** and **144** by Hayashi and co-workers[75] to give only the regioisomers **183** and **184**, respectively (eq 52), with even better ee's (90−99%) than those obtained for the dihydrofuran **118** in the presence of Pd−(*R*)-BINAP catalyst.[75] With BITIANP **31** as the chiral ligand, the 5-cyclohexenyl-2-pyrroline derivative **183** was obtained in 73% yield and 91% ee within 18 h, although with lower regioselectivity (**183**:**185**, 4:1) in comparison to the reaction of **173** with aryl triflate using BITIANP ligand **31**.[84]

2.2.3. Intermolecular Arylation and Alkenylation of Alkenes

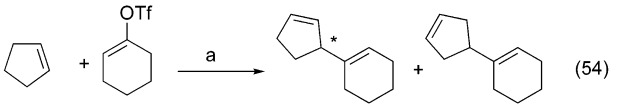
The poor regio- and enantioselectivity observed earlier in the asymmetric arylation of cyclopentene **190** with (*R*)-BINAP as ligand due to extensive double bond migration was dramatically improved by using the phosphinooxazoline ligand **121b**, which exhibits remarkable resistance toward isomerization of the first formed alkenes. Thus, the best ee (91%) with the highest conversion and yield for the product **187** was obtained in DMF as a solvent, whereas the less polar THF resulted in a somewhat lower ee (86%), although with better regioselectivity (**187**:**188**, 99:1) (eq 53).[18a,60]

Recently, the corresponding benzoxazine and bicyclic phosphinophenyloxazoline ligands **130**[71] and **128**[68] have been examined in the same reaction to give **187** with reasonably good ee's but low yield with **130** (eq 53). Similarly, the 3-(cyclohexenyl)cyclopentene **189** could be obtained by cyclohexenylation of **186** in high yield and ee (89%; **189**:**190**, 98:2) under identical conditions in benzene (eq 54).[18] Gilbertson and co-workers[68] have reported formation of **189** with 94% ee by using phosphinophenyloxazoline ligand **128**, although with low regioselectivity. On the other hand, the arylation of cyclohexene was found to be rather sluggish, requiring a higher temperature and a prolonged reaction time (6 days) to afford **192** in good yield but with low ee (43%) (eq 55).[18]



186 187 188

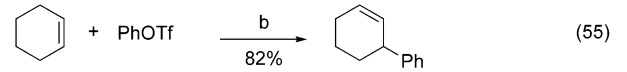
Pd [mol%]	L * [mol%]	solvent	temp [ºC]	time [d]	yield [%]	191:192	*ee* 191 [%]
3	**121b** (6)	DMF	70	5	85	96 : 4	91 (*R*)
3	**121b** (6)	THF	70	5	80	99 : 1	86 (*R*)
1.5	**130** (5)	THF	50	5	29	98 : 2	84 (*S*)
2.5	**128** (6)	C_6H_6	95	1	83	>99	78 (*R*)



186 139 189 190

entry	L*	solvent	temp [ºC]	time	tot. yield [%]	189:190	*ee* 189 [%]
1	**121b**	THF	75	4 d	82	65 : 35	73 (*R*)
2	**121b**	C_6H_6	40	5 d	70	98 : 2	89 (*R*)
3	**128**	C_6H_6	70	2 d	78	48 : 30	94 (*R*)
4	**128**	THF	70	22 h	100	96 : 4	69 (*R*)

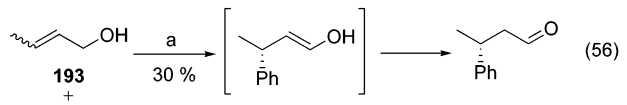
a) Pd(dba)$_2$ (2.5–3 mol%), L*(6 mol%), *i*Pr$_2$NEt, solvent



191 192: 43% *ee*

b) Pd(dba)$_2$ (5 mol%), **121b** (10 mol%), C_6H_6, *i*Pr$_2$NEt, 90 ºC, 6 d

Uemura and co-workers have recently reported the enantioselective phenylation of *cis*- and *trans*-crotyl alcohols **193** with iodobenzene using chiral phosphinite-oxazoline ligands **125** derived from D-glucosamine (eq 56).[66] Although the observed enantioselectivity for



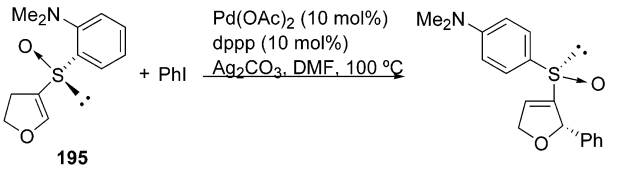
193 + PhI 194: 17 % *ee*

a) Pd$_2$(dba)$_3$ (5 mol%), **125c** (5.6 mol%), Ag_2CO_3, THF, 65 ºC, 3 d

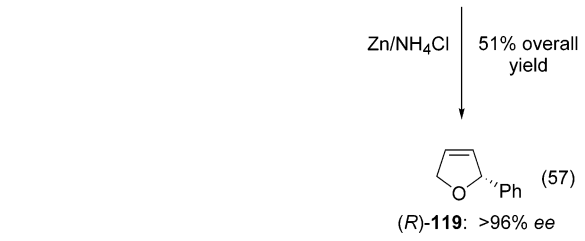
the product 3-phenylbutanal was only 17%, the reaction represents the first example of an enantioselective intermolecular arylation of prochiral acyclic alkenes.[66]

Although auxiliary controlled reactions are not covered in this review, the elegant use of a sulfoxide as a chiral element displaying high induction in asymmetric intermolecular Heck reactions (**195** and **196**), as demonstrated by Carretero in two recent publications,[86] is worth mentioning (eq 57).

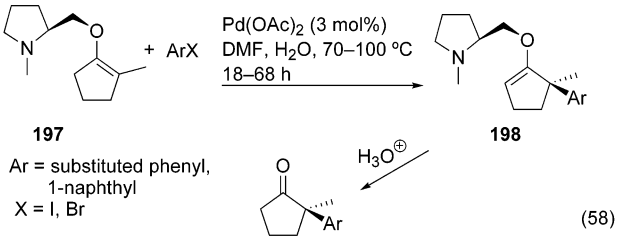
Hallberg and co-workers[87] have reported a novel, highly asymmetric chelation controlled intermolecular Heck reaction involving the arylation of prolinol vinyl ether **197** (derived from (*S*)-1-methyl-2-pyrrolidine-methanol) in the presence of a phosphine-free palladium catalyst to afford the corresponding 2-aryl-2-methylcyclopentanones **199** (after hydrolysis of **198**) with excellent regio- and enantioselectivity (eq 58). Larhed and co-workers[88a] have recently reported the first microwave-accelerated intermolecular asymmetric Heck process, an achievement which is very much desirable in view of the long reaction times reported especially for diphenylphosphinooxazoline



195 (2*S*,S*R*)-**196**: 92% *de*



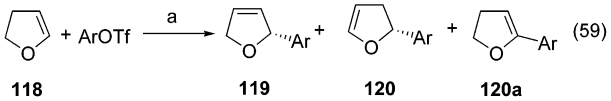
(*R*)-**119**: >96% *ee*



197 198

199a: 45–78%, 90–98% *ee*
Ar = 2-MeOC$_6$H$_4$, 67%, 98% *ee*

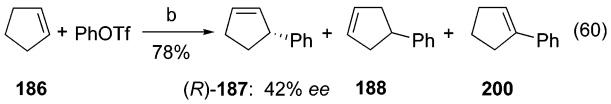
ligands **121**. With the aid of controlled dielectric heating, significant enantioselectivities of up to 92% ee were obtained for the asymmetric arylation of **118** utilizing a thermostable palladium−phosphinooxazoline (**121b**) catalyst system (eq 59) and the reaction time of 4−5 days was reduced to several hours and minutes. The electronic properties of aryl triflates were found to be important for the reactivity.



118 119 120 120a

entry	Ar	time [h]	yield [%]	isomeric ratio		*ee* (**119** or **120**) [%]
1	Ph	3	64	**119/120a**	90 : 10	90
2	4-MeOC$_6$H$_4$	55 min	58	**119/120a**	90 : 10	90
3	4-MeOC$_6$H$_4$	4	85	**119/120a**	100 : 0	88
4	1-naphth	8	80	**119/120a**	100 : 0	92
5	Ph[a]	10 min	53	**120/119**	94 : 6	50

[a] with (*R*)-BINAP



186 (*R*)-**187**: 42% *ee* 188 200

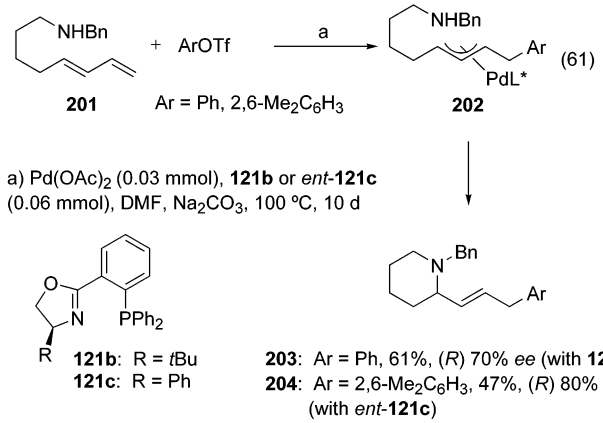
ratio **185** : (**188**+**200**) 98:2

a) microwave, Pd$_2$(dba)$_3$ (3 mol%), **121b** (6 mol%), C_6H_6, proton sponge, 120–160 °C
b) **121b** (6 mol%), Pd$_2$(dba)$_3$ (3 mol%), proton sponge, C_6H_6, 140 °C, 4 h

Thus, in this novel asymmetric reaction, the election-rich 4-methoxyphenyl triflate reacted to produce high yields (up to 85%) and a high ee value (88%) for pure **119** (Ar = 4-MeOC$_6$H$_4$, entry 3), whereas the use of electron-poor 4-cyanophenyl triflate provided

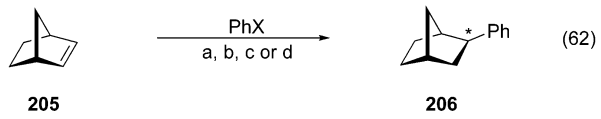
only small amounts of arylated product. On the other hand, sterically demanding 1-naphthyl triflate furnished the highest ee (92%) but also the lowest reaction rate (entry 4). It is noteworthy that small amounts of nonchiral **120a** without **120** were formed in all of these reactions (entries 1−4). The use of (*R*)-BINAP allowed a dramatic time reduction (10−30 min), but a significantly lower yield and enantioselectivity was encountered (entry 5). Microwave-induced arylation of cyclopentene resulted mainly in the formation of **187** with only traces of the isomers **188** and **200** (1−2%). The product **188** was formed in high yield (78%) but with low ee (42%) after 4 h of microwave heating at 140 °C (eq 60), in comparison to 5 days of heating in the classical reaction (eq 53). Thus, although the stereoselectivity for phenylation of **118** was reduced from 97% (70 °C) to 90% (140 °C), the reaction time is reduced from days to hours. In the future, new thermostable palladium−chiral ligand systems may be explored in the light of high enantioselectivities (99% ee) reportedly obtained in microwave flash-heated asymmetric allylic substitution after only 30 s of irradiation.[88b]

A novel enantioselective two-component domino Heck−allylic amination reaction of the α,ω-amino-1,3-diene **201** to give the chiral piperidine derivatives **203** and **204** has been recently described by Helmchen and co-workers.[57] Chiral phosphinooxazoline ligands **121b**,**c** were found to be more effective in this transformation in comparison with (*R*)-BINAP, to give **118** with 80% ee in moderate chemical yields (eq 61).

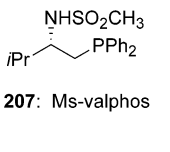


3. Hydroarylation/Alkenylation of [2.2.1]Bicycles

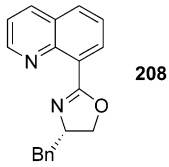
The enantioselective hydroarylation/alkenylation of alkenes involves an oxidative addition and an alkene insertion step as in the Heck reaction, followed by reductive elimination of the Pd species instead of a β-hydride elimination with the generation of a stereogenic center. The asymmetric hydroarylation of norbornene **205** with various aryl iodides was first reported by Brunner and Kramler in 1991,[89] to give *exo*-2-arylnorbornanes with a maximum ee of 38−41% with (−)-Norphos as chiral ligand. In subsequent studies, Achiwa and co-workers[90] obtained **206** with enantioselectivities of up to 74% by employing chiral (β-*N*-sulfonylaminoalkyl)phosphines such as Ms-valphos **207** (eq 62).[90]



a) PhOTf, $Pd(OAc)_2$, **207**, DMSO, Et_3N, HCO_2H, 65 °C, 20 h, 81%, 74% *ee*
b) PhI, $Pd_2(dba)_3$, **208**, Et_3N, HCO_2H, DMSO, 25 °C, 58 h, 60%, 73% *ee*
c) PhOTf, **209a** (3 %), HCO_2H, Et_3N, DMF, rt, 24 h, 70%, 75% *ee*
c) PhOTf, **209b** (3 %), HCO_2H, Et_3N, DMF, rt, 24 h, 60%, 74% *ee*



207: Ms-valphos



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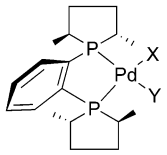
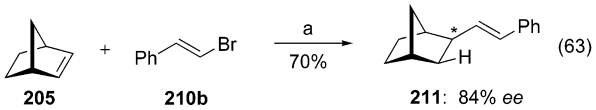
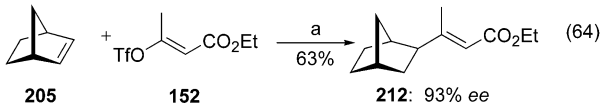


209a: X = Y = OAc
209b: X = Ph, Y = I



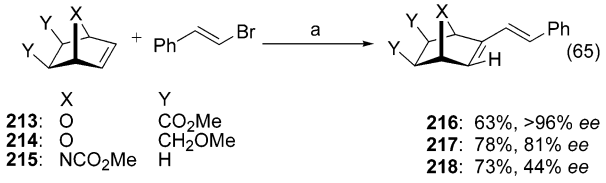
a) Pd [(*R*)-BINAP]$_2$ (1 mol%), $ClCH_2CH_2Cl$, Et_3N, HCO_2H, 40 °C, 7 d



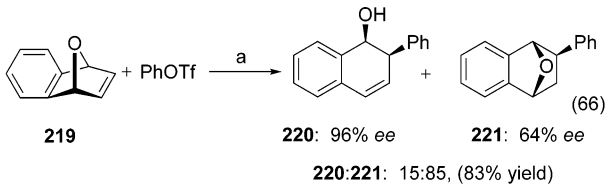
a) Pd [(*R*)-BINAP]$_2$ (3 mol%), $ClCH_2CH_2Cl$, proton sponge, HCO_2H, 40 °C, 86 h

Zhou and co-workers[91] have also studied the hydroarylation of **205** in the presence of a Pd complex of the chiral quinolyloxazolines **208** to yield **206** with a similar range of enantioselectivity, although in decreased yields (eq 62). Kaufmann and co-workers have reported the highest ee of 86.4% for this reaction using phenyl nonaflate and Achiwa's ligand, but in very low yield.[92] Recently, Pregosin has used Pd complexes of (*R*,*R*)-MeDUPHOS **209** for hydrophenylation of norbornene to give **206** in 70% yield and 75% ee.[93] The alkenylation of norbornene with β-halostyrenes and alkenyl triflates has been examined by Hayashi and co-workers (eqs 63 and 64).[94] Interestingly, the hydroalkenylation of **205** with β-bromostyrene **210** in the presence of the Pd−(*R*)-BINAP catalyst proceeded efficiently in 1,2-dichloroethane with enhanced enantioselectivity (84%) compared to the arylation (eq 63). On the other hand, the reaction with β-iodostyrene gave only the racemic product **211** in 91% yield. The alkenylation with triflate **152** was found to be most efficient in these reactions, and the alkenylation product **212** was formed in 63% yield with a very high enantiomeric excess (93%) (eq 64). The hydroalkenylation studies were also extended to 7-oxa- (**213** and **214**) and 7-aza- (**215**) norbornene systems with β-bromostyrene and Pd−(*R*)-BINAP catalyst (eq 65), which yielded the hydroalkenylated products (**216** and **217**) in high ee's (81−96%) with

oxabicyclics, whereas a low ee (44%) was obtained for the azabicyclic derivative **218**.



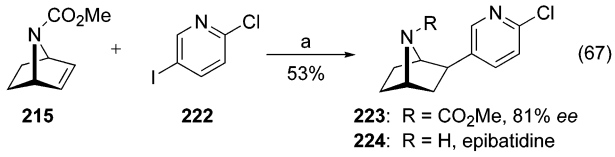
a) Pd [(*R*)-BINAP]$_2$ (1 mol%), Et_3N, HCO_2H, $ClCH_2CH_2Cl$, 40 °C, 168 h



a) Pd [(*R*)-BINAP]$_2$, $Na^{\oplus}HCO_2^{\ominus}$, DMF, 55 °C, 7 d

Fiaud and co-workers[95] have examined the Pd-catalyzed asymmetric hydrophenylation of 1,4-dihydro-1,4-epoxynaphthalene **219** with iodobenzene and phenyl triflates in the presence of various chiral ligands to give a mixture of dihydronaphthalene derivative **220** and the tricyclic product **221** in varying yields and ee's, with the highest ee of 96% for the minor product **220**, obtained using Pd−(*R*)-BINAP catalyst (eq 66).

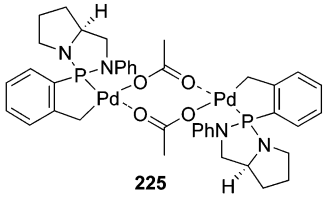
Kaufmann and co-workers have recently reported the enantioselective synthesis of the both enantiomers of *N*-protected epibatidine **223** by enantioselective reductive Heck-type arylation of 7-azanorbornene derivative **215** with iodopyridine **222** (eq 67).[96] Under optimized conditions, enantiomeric ex-



a) Pd(OAc)$_2$, (*R*)-BINAP, THF, Et_3N, HCO_2H, 65 °C, 5 d

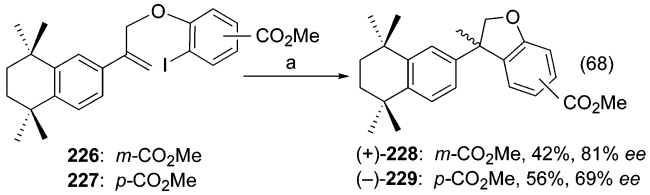
cesses between 72 and 81% and a chemical yield of up to 53% could be obtained with Pd−(*R*)-BINAP. Also, by using either the (*R*)- or the (*S*)-BINAP ligand, both enantiomers of *N*-protected epibatidine **223** were easily accessible with almost the same degree of enantioselection. Using the quinolylisoxazoline **208** as the chiral ligand, Zhou and co-workers have obtained **223** in 67% yield but with lower ee (51%).[91c]

Buono and co-workers[97a] have described the synthesis of the new phosphapalladacycle **225**, bearing



a stereogenic phosphorus atom, and its use in the asymmetric hydroarylation of norbornene **205** to give **206**. They reported a turnover number (TON) of up to 10^{10} with an enantioselectivity of 25% ee of 2-phenylnorbornane **206**. However, their paper has recently been withdrawn.[97b]

An enantioselective domino reaction consisting of an intramolecular Heck cyclization−hydride capture process has been reported by Diaz and co-workers[98] for the synthesis of novel conformationally restricted retinoids (eq 68). Thus, the substrates **226** and **227**

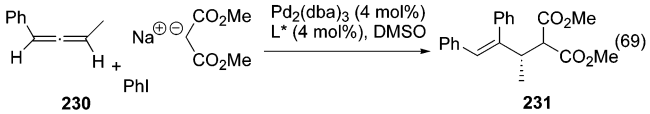


a) Pd(OAc)$_2$ (10 mol%), (*R*)-BINAP (20 mol%), $CaCO_3$, HCO_2Na, Ag-zeolites, CH_3CN, 60 °C, 8 h

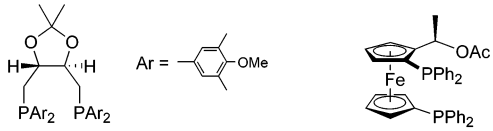
underwent the desired enantioselective reductive cyclization in the presence of Pd−(*R*)-BINAP to give the product retinoids **228** and **229** with 81 and 69% ee respectively, although in moderate yields.

4. Carbopalladation−Addition/Cyclization of Allenes

Asymmetric carbopalladation of allenes followed by nucleophilic capture (inter- or intramolecular) of intermediate β-aryl π-allylpalladium complexes is a potentially useful reaction for the synthesis of enantioenriched hetero- and carbocycles as well as α,β-functionalized olefins. Hiroi and co-workers have recently reported a direct palladium-catalyzed asymmetric α,β-functionalization of racemic allene **230** by reaction with iodobenzene and malonate carbanion in the presence of various chiral ligands to give the olefins **231** as products with very good enantioselectivity (eq 69).[99] The highest ee of 96% was obtained with (*S*)-BINAP ligand, whereas with the ferrocenyl ligand (*R*,*S*)-BPPFOAc, the olefin (*S*)-**231** was obtained with comparable enantiopurity (95%) but in higher yield.



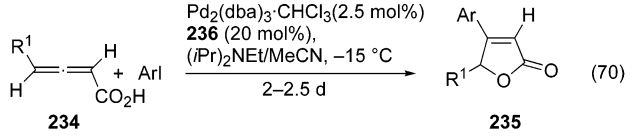
L*	temp [°C]	time [h]	yield [%]	*ee* [%]
(*S*)-BINAP	40	24	42	96
(4*R*,5*R*)-MOD-DIOP	66	18	89	90
(*R*)-(*S*)-BPPFOAc	66	18	77	95



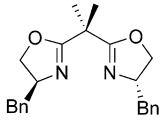
(4*R*,S*R*)-(+)-MOD-DIOP (*R*)-(*S*)-BPPFOAc

Only a few examples of asymmetric induction in intramolecular π-allyl displacement are known in the literature.[100] In a recent study on the synthesis of butenolides via Pd-catalyzed coupling−cyclization of

2,3-allenoic acids[101a] with aryl iodides, Ma and co-workers have investigated the catalytic enantioselective version of this reaction (eq 70).[101b] Thus, Pd-

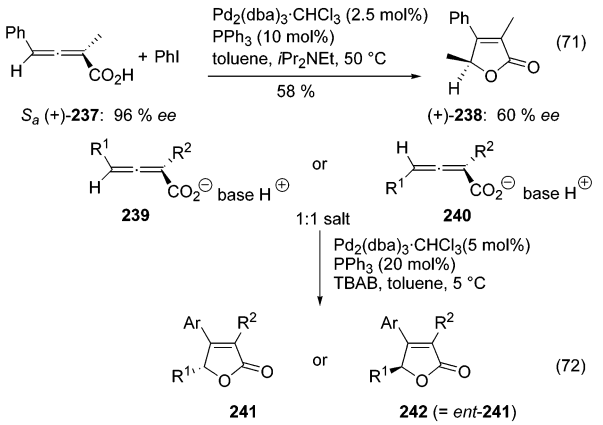


R^1	ArI [eq.]	yield [%]	ee [%]
*n*Hept	Ph	52	52
*n*Bu	4-MeC$_6$H$_4$	44	53
*n*Bu	4-MeOCOC$_6$H$_4$	53	53



236

catalyzed carbopalladation of allenoic acid **234** with aryl iodides in the presence of bisoxazoline **236** as chiral ligand furnished the lactones **235** in reasonable yields with moderate ee of up to 53%.[101b] On the other hand, in a recent parallel study, the same workers have described a highly efficient chirality transfer in Pd-catalyzed coupling−cyclization of aryl iodides with salts of 2,3-allenoic acids and chiral amines (eq 72).[102]

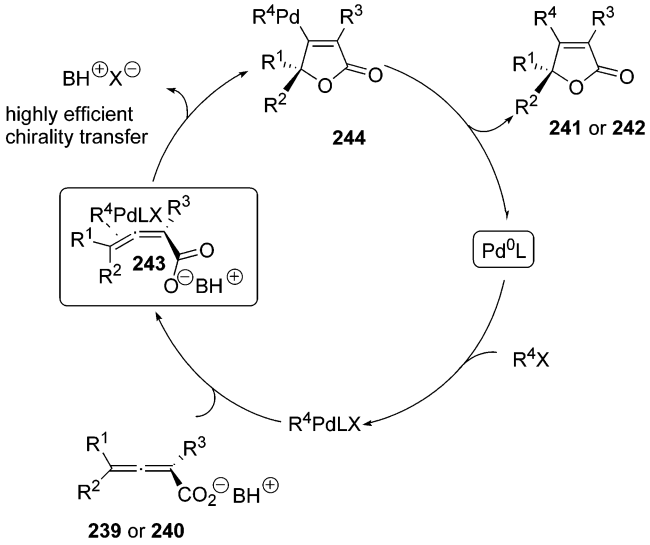


entry	R^1	R^2	base	acid-base salt	Ar^2I	time [h]	yield **242** [%]	*ee* **242** [%]
1	Ph	Me	A	(+)-**240a**	Ph	48	90 (*S*)-**242a**	91
2	Ph	Me	B	(+)-**240b**	Ph	72	60 (*S*)-**242a**	93
3	Ph	Me	C	(−)-**240b**	Ph	60	66 (*R*)-**242a**	96
4	Ph	Me	C	(−)-**240b**	4-MeC$_6$H$_4$	60	72 (*R*)-**242b**	98
5	Ph	*n*Pr	A	(+)-**240c**	Ph	60	72 (*S*)-**242c**	91
6	*n*Hept	H	A	(+)-**240d**	Ph	48	55 (+)-**242d**	94
7	Ph	Me	C	(−)-**240b**	4-(CO$_2$Me)C$_6$H$_4$	60	58 (*R*)-**242e**	94

Base, A = L-(–)-cinchonidine; B = L-(–)-α-methylbenzylamine; C = D-(+)-α-methylbenzylamine

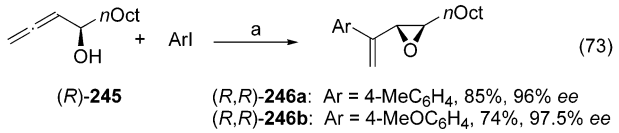
Earlier studies with chiral allenoic acid **237**, reacting it with PhI in the presence of Pd^0 catalyst and Hünig's base, gave butenolide **238** in only 58% yield with 60% ee (eq 71). However, in a different approach, the Pd-catalyzed transformation of the corresponding 1:1 salts of chiral 2,3-allenoic acids (**239** or **240**) and l-(−)-cinchonidine or D-(+)/L-(−)-α-methylbenzylamine with various aryl iodides gave the butenolides (**241** or **242**) in good yields and in >90% ee. The highest ee of 98% was obtained with the D-(+)-α-methylbenzylamine salt (entry 4). A probable

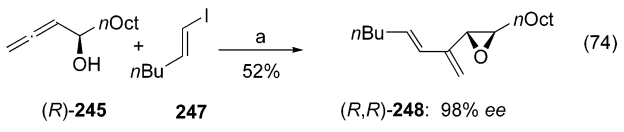
Scheme 5. Mechanism of the Highly Efficient Chirality Transfer in the Pd^0-Catalyzed Coupling−Cyclization of Allenoic Acids 239 and 240, Respectively, to Butenolides 241 and 242, Respectively



mechanism involving oxidative coordinative cyclization of the intermediate **243**, followed by reductive elimination of Pd^{0}L from the intermediate **244** (Scheme 5), has been proposed for this highly efficient Pd-catalyzed enantioselective synthesis of 3-arylbutenolides through chirality transfer.

Also noteworthy is another example of efficient chirality transfer, reported by Ma and co-workers,[103] in a highly enantioselective synthesis of *trans*-2,3-substituted vinyloxiranes **246a**,**b** and **248** by Pd-catalyzed coupling−cyclization of chiral 2,3-allenol **245** with aryl/alkenyl iodides, with the highest ee of 98% for the epoxide **248** (eqs 73 and 74).[103]

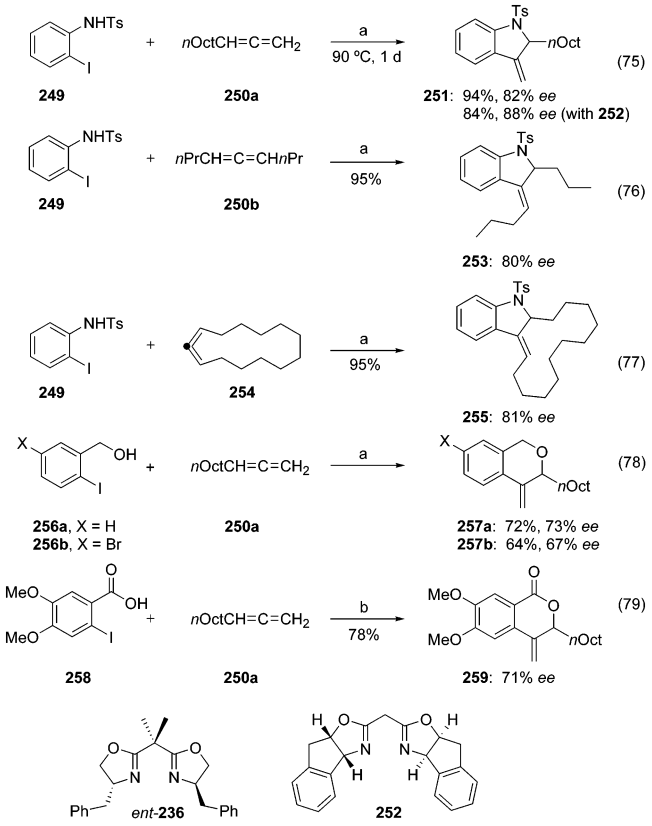




a) Pd(PPh$_3$)$_4$ (5 mol%), K$_2$CO$_3$, DMF, 55 °C, 14 h

Larock and Zenner have recently described a palladium-catalyzed enantioselective hetero- and carboannulation of allenes using functionally substituted aryl and vinyl iodides to yield five- and six-membered heterocycles in good yields with high regioselectivity and a moderate to high level of enantioselectivity.[104a] The generality of this process has been demonstrated by the use of various nucleophilic substituents as tosylamides, alcohols, phenols, carboxylic acids, and stabilized carbanions together with both cyclic and acyclic allenes (eqs 75−82).

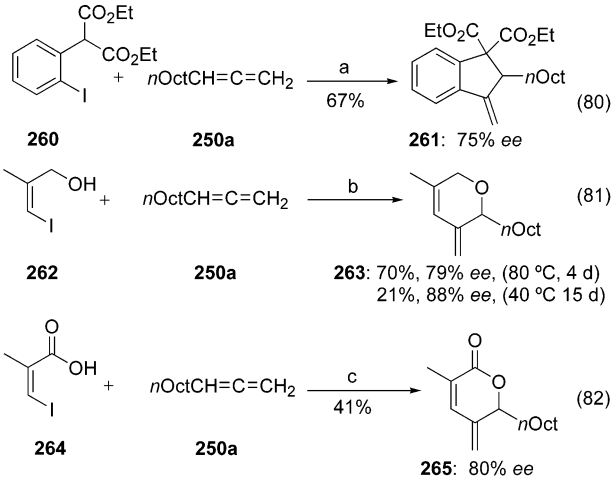
The best ee's were obtained using the bisoxazoline ligands developed by Pfaltz and others, particularly



a) $Pd(OAc)_2$ (5 mol%), *ent*-**236** (10 mol%), Ag_3PO_4, DMF, 80–90 °C, 1–4 d
b) $Pd_2(dba)_3$ (5 mol%), *ent*-**236** (5 mol%), Ag_3PO_4, DMF, 40 °C, 6 d

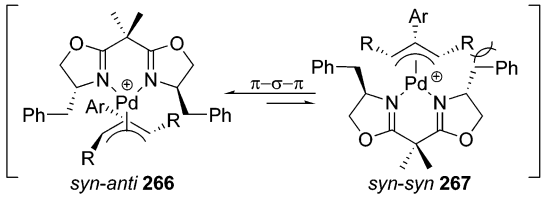
236, which gave the exomethylene indole derivative **251** from **249** in 94% yield and 82% ee (eq 75), whereas in the presence of the chiral ligand **252** under the same conditions, the product **251** could be obtained in an even higher enantiomeric excess of 88%. In general, internal allenes such as 4,5-nonadienes **250b** gave cyclized products with lower levels of enantioselectivity than terminal allenes, except for the model system **249** (eq 76). Extension of this process to other nucleophilic substrates could not be achieved to the same level of enantioselection obtained in the model system **249** (eq 75). Thus, the 2-iodobenzyl alcohol **256a** reacted with 1,2-undecadiene **250a** to give the cyclized product **257a** in 72% yield, with the highest ee of 73% (eq 78). The cyclization of substituted 2-iodobenzoic acids with 1,2-undecadiene **250a** gave the highest ee of 71% for the product **259**, which was formed in a good yield (eq 79). Carboannulation has also been carried out using this methodology with the substrate diethyl 2-iodophenyl malonate **260** to give the indane **261** in 67% yield and 75% ee (eq 80).

Extension of this reaction to six-membered heterocycles using vinyl iodides **262** and **264,** bearing an alcohol and a carboxylic acid functionality, respectively, followed the same trend found with the aryl analogues, with the highest ee of 88% for **263**, although a poor yield (21%), which could not be increased even by employing a reaction time of 15 days (eqs 80 and 81). The observed enantioselection in these cycloannulation reactions has been rationalized in terms of minimization of the steric interaction between the benzyl groups of the chiral ligand **236** and the terminal alkyl substituent (R) of the π-



a) $Pd_2(dba)_3$ (10 mol%), *ent*-**236** (10 mol%), Ag_3PO_4, DMF, 90 °C, 3 d
b) $Pd(OAc)_2$ (5 mol%), *ent*-**236** (10 mol%), Ag_3PO_4, DMF
c) $Pd_2(dba)_3$ (5 mol%), *ent*-**236** (10 mol%), Ag_3PO_4, DMF, 40 °C, 3 d

allylpalladium intermediate, leading to preferential formation of the diastereomeric intermediate **266** over **267**.[104a] Assuming the backside nucleophilic



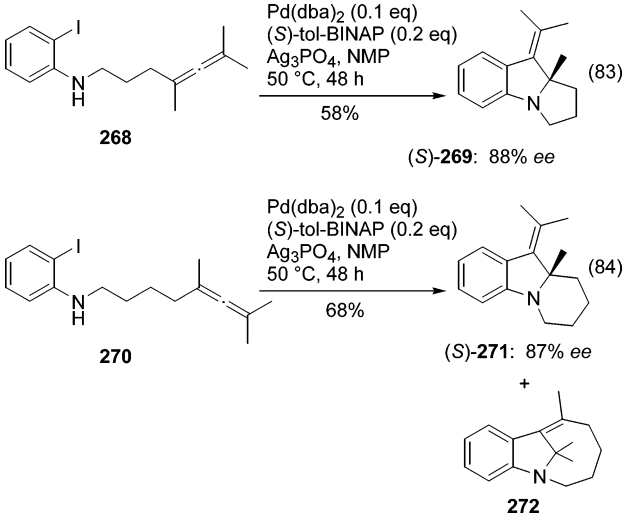
displacement on **266**, the mechanistic model would predict an (*S*) absolute configuration for the observed product, which was supported by X-ray determination of one of the benzopyrans **257b** (eq 78) shown to have (*S*) absolute configuration.

The previous examples of carbopalladation–cyclization of allenes involve reactions between two components with a nucleophilic moiety present either in the allene function (eqs 70–74) or ortho to the aryl iodide (eqs 75–82). Recently, Hiroi and co-workers have reported a novel domino intramolecular asymmetric carbopalladation–amination of allenes **268** and **270**, bearing an *o*-iodophenylamino group which allows a facile entry to chiral bicyclic indoles (**269** and **271**) (eqs 83 and 84).[105]

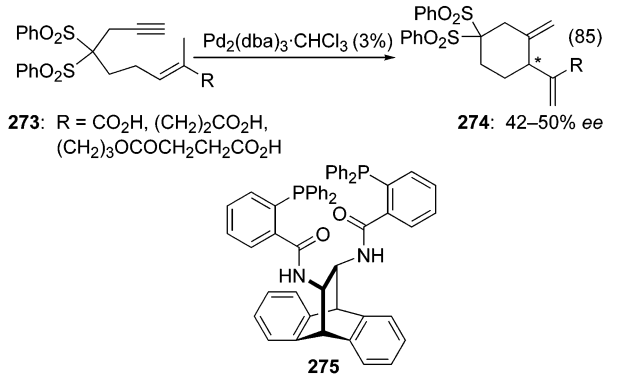
Thus, (*S*)-tol-BINAP ligand was found to be most effective for this unusual cyclization, affording indoles **269** (58%) and **271** (68%) with enantiomeric purity of up to 88 and 87%, respectively. The formation of a small amount of 1,4-(dimethylmethano)-5-methyl-1-azabenzo[2.3]cyclonon-4-ene derivative **272** was unexpectedly observed in the carbopalladation–amination of allene **270** (eq 84).[105]

5. Enyne Cycloisomerizations

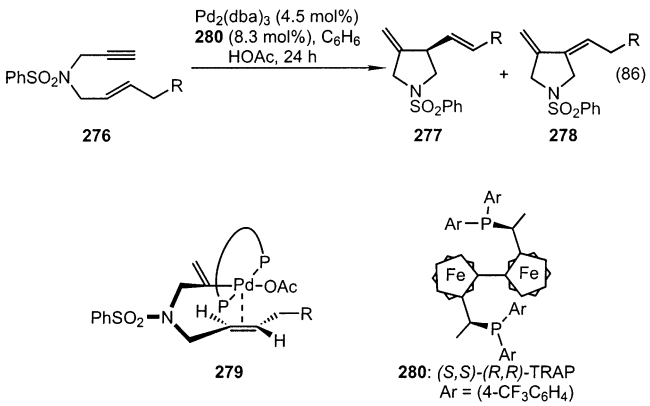
The palladium-catalyzed enyne cycloisomerization developed by Trost and co-workers is a powerful tool for the synthesis of cyclic and polycyclic compounds.[106–108] However, examples of the corresponding enantioselective reactions are limited, and the earlier attempts with chiral carboxylic acids (Mosher's acid, α-methoxy-α-trifluoromethylphenyl



acetic acid, MTPA) gave fairly low induction.[109] Subsequent use of amide−diphosphane chiral ligand **275** with a few chiral (double stereodifferentiation) and achiral substrates such as **273** yielded cyclized products **274** with maximum ee's ranging between 42 and 50% (eq 85).[110]



A more efficient enantioselection was achieved with chiral diphosphane ligands such as (*S*,*S*)-(*R*,*R*)-TRAP bisferrocenyldiphosphanes **280**, furnishing the 1,4-dienes **277** from the 1,6-enynes **276** with moderate to high enantioselectivities (eq 86).[111]



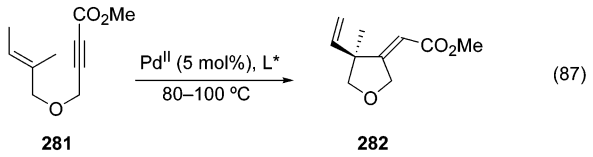
In general, the use of ligand **280** and its analogues with substituted aryl groups increased the regio- and enantioselectivity for the desired product **277**, but decreased the reaction rates, resulting in low chemical yields. The best results were obtained with the ligand **280** (Ar = 4-$CF_3C_6H_4$) at 0 °C to afford the 1,4-diene **277** (R = $SiMe_3$) in 24% yield with 76% ee (Table 8, entry 1).

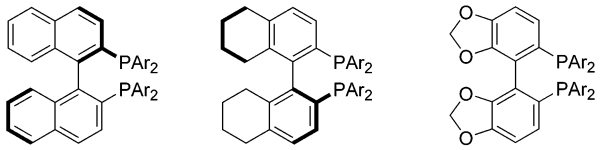
Table 8. Enantioselective Cycloisomerization of 1,6-Enynes 276 Catalyzed by the Pd Complex of 280 (Eq 86)

entry	R	temp (°C)	**277**:**278**	yield **277** (%)	ee (%)
1	$SiMe_3$	0	>98:2	24	76 (*R*)
2	$SiMe_2Ph$	0	>98:2	27	66 (*R*)
3	CH_2SiMe_3	25	3.5:1	68	95 (*R*)
4	$(CH_2)_2SiMe_3$	35	>15:1	71	65 (*R*)
5	*n*Pent	35	6.8:1	73	67 (*R*)
6	Bn	35	5:1	75	75 (*R*)

The highest ee of 95% was obtained with the substrate bearing a homoallylsilyl group (entry 3), although with lower regioselectivity (**277**:**278**, 3.5:1), with appreciable formation of the 1,3-diene **278**. A trans coordination was shown to be essential in the Pd complex **279**, whereas cis chelating phosphanes such as CHIRAPHOS, DIOP, BPPFA, and PPF led to selectivities of only 6−15% ee, with an overall conversion of 56−85%.

In a very recent paper, Mikami and co-workers[112] have described a highly efficient Pd-catalyzed enantioselective ene-type carbocyclization of 1,6-enyne **281**, leading to the enantiopure five-membered furan **282** with a quaternary chiral center with ee's >99% (eq 87).





8a: (*R*)-BINAP, Ar = Ph
8c: (*R*)-tol-BINAP, Ar = 4-MeC_6H_4
283a: (*S*)-H_8-BINAP (Ar = Ph)
283b: (*S*)-xylyl-H_8-BINAP (Ar = 3,5-$Me_2C_6H_3$)
284a: (*R*)-SEGPHOS (Ar = Ph)
284b: (*S*)-xylyl-SEGPHOS (Ar = 3,5-$Me_2C_6H_3$)

In a detailed investigation, these workers have shown that the insufficient catalytic activity and the low level of asymmetric induction observed earlier in these cyclizations using chiral BINAP ligand and $Pd(OAc)_2$ or $Pd_2(dba)_3$ can be dramatically improved by using $Pd(CF_3CO_2)_2$. Thus, the Pd-catalyzed cyclization of **281** to give the 1,4-diene (*S*)-**282** was successfully achieved in quantitative yield and with high enantioselectivity (93% ee, Table 9, entry 1) by using $Pd(CF_3CO_2)_2$ and 10 mol % (*R*)-BINAP.

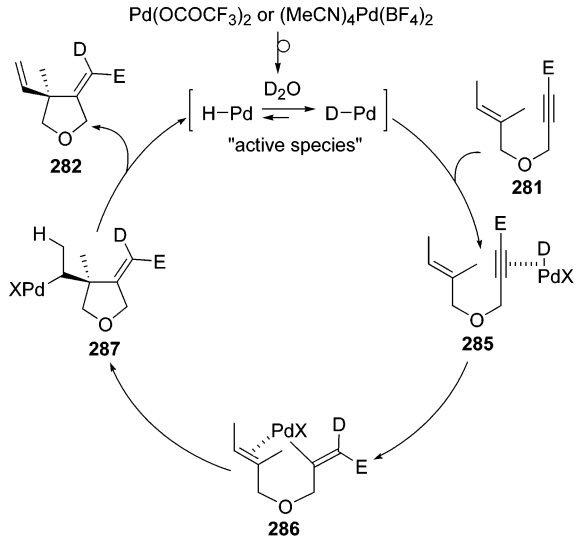
Furthermore, in polar solvents such as DMSO, the reaction could be performed at a lower temperature (entry 2) and in a shorter time period, but a decrease in enantioselectivity was observed compared to that found for the transformation in nonpolar solvents (entry 1 versus entry 2). Similarly, the dicationic Pd^{II} species $[(MeCN)_4Pd](BF_4)_2$, in combination with (*R*)-BINAP, also accelerates the reaction dramatically in

Table 9. Enantioselective Ene-Type Carbocyclization of 281 Catalyzed by Pd Complexes of Modified BINAP Ligands (Eq 87)

entry	L* [a]	Pd species[b]	solvent	time (h)	yield (%)	ee (%)
1	(*R*)-BINAP (**8a**)	$Pd(OCOCF_3)_2$	C_6D_6	24	>99	93 (*S*)
2	(*R*)-BINAP (**8a**)	$Pd(OCOCF_3)_2$	DMSO	16	>99	72 (*S*)
3	(*R*)-BINAP (**8a**)	$[(MeCN)_4Pd](BF_4)_2$	DMSO	6	>99	73 (*S*)
4	(*R*)-tol-BINAP (**8c**)	$Pd(OCOCF_3)_2$	C_6D_6	43	>99	94 (*S*)
5	(*S*)-H_8−BINAP (**283a**)	$Pd(OCOCF_3)_2$	C_6D_6	48	>99	95 (*R*)
6	(*R*)-SEGPHOS (**284a**)	$Pd(OCOCF_3)_2$	C_6D_6	37	>99	>99 (*S*)
7	(*R*)-SEGPHOS (**284a**)	$[(MeCN)_4Pd](BF_4)_2$	DMSO	6	>99	90 (*S*)
8	(*S*)-xylyl-H_8−BINAP (**283b**)	$Pd(OCOCF_3)_2$	C_6D_6	20	>99	12 (*R*)
9	(*S*)-xylyl-H_8−BINAP (**283b**)	$[(MeCN)_4Pd](BF_4)_2$	DMSO	14	>99	94 (*R*)
10	(*S*)-xylyl-SEGPHOS (**284b**)	$[(MeCN)_4Pd](BF_4)_2$	DMSO	14	>99	96 (*R*)

[a] L* (10 mol %). [b] Pd species (5 mol %).

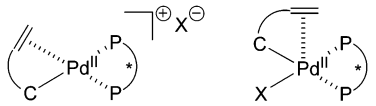
Scheme 6. Catalytic Cycle Involving H (D)−Pd as the Active Species (Eq 87)



DMSO but with lower enantioselectivity (entry 3). Further exploration of the modified BINAP ligands with either $Pd(CF_3CO_2)_2/C_6D_6$ or the $[(MeCN)_4Pd](BF_4)_2$/DMSO system led to a remarkable improvement in enantioselectivity. The (*R*)-tol-BINAP **8c** and (*S*)-H_8-BINAP **283a** ligands were found to be as effective as (*R*)-BINAP, furnishing **282** in 94 and 95% ee, respectively, under similar conditions (entries 4 and 5). Virtually complete enantioselectivity was achieved with (*R*)-SEGPHOS ligand **284a** in benzene, which gave **282** in quantitative yield (entry 6). (*R*)-SEGPHOS **284a** was also found to be more effective than (*R*)-BINAP in polar solvents such as DMSO, exhibiting higher enantioselectivity (entry 7 vs entries 2 and 3). On the other hand, the use of the sterically more demanding (*S*)-xylyl-H_8-BINAP ligand **283b** resulted in a significant decrease of enantioselectivity (entry 8), presumably due to its bulkiness. However, in the presence of $[(MeCN)_4Pd](BF_4)_2$/DMSO, dramatic improvement in enantioselectivity was observed (entry 9), in contrast to entry 8. Combination of the SEGPHOS skeleton and the bulky xylyl substituent as in the (*S*)-xylyl-SEGPHOS ligand **284b** led to a highly enantioselective catalyst (96% ee), even with the $[(MeCN)_4Pd](BF_4)_2$/DMSO system (entry 10).

In a detailed mechanistic study,[112] the same workers have demonstrated the existence of hydride−palladium (H−Pd) as the active species in this cyclization by carrying out the reaction in excess D_2O, and the possible catalytic cycle is shown in Scheme 6.

The coordination of D−Pd species to acetylene **285** is followed by an insertion (**286**), a cyclization (**287**), and a β-H elimination to give the product **282** after regeneration of the H−Pd species. The observed effect of the solvent polarity on both the enantioselectivity and the catalytic activity, using either $Pd(CF_3CO_2)_2$ or $[(MeCN)_4Pd(BF_4)_2]$ as the cationic Pd^{II} source, has been explained on the basis of the formation of the cationic four-fold-coordinated intermediate **288** or the



neutral five-fold-coordinated intermediate **289**, depending on the polarity of the solvent and the nature of the counteranion in the Pd^{II} species (i.e., $CF_3CO_2^-$ and BF_4^-). Under polar conditions, the reaction proceeds via the four-coordinated transition-state intermediate **288a** or **288b** to afford either the product (*S*)-**282** and (*R*)-**282**, respectively (Figure 1).

However, the transition state **288b** is less favorable due to the steric repulsion between the terminal Me group in substrate **281** and the equatorial Ph group of (*R*)-BINAP or its analogue. Thus, only (*S*)-**282** is formed from the more favorable transition state **288a**, avoiding this repulsion. Under less polar conditions, a repulsive interaction exists between the terminal Me group of the substrate **281** and the equatorial phenyl group of (*R*)-BINAP in the five-fold-coordinated neutral transition state **289b**. Therefore, the reaction takes place entirely via the more favorable transition state **289a** to afford (*S*)-**282** (Figure 1).

In a recent paper, Mikami and co-workers developed the first efficient asymmetric synthesis of six-membered quinoline derivatives bearing a quaternary carbon center or a spiro ring, by the ene-type cyclization of ortho-substituted 1,7-enynes catalyzed by cationic BINAP−Pd^{II} complex (eqs 88−91).[113] Thus, the cyclization of the substrates **290a**,**b** in the presence of cationic Pd^{II} catalyst such as $[(MeCN)_4Pd](BF_4)_2$/(*S*)-BINAP and formic acid in DMSO led to quinolines **291a**,**b** with a quaternary carbon center as *single enantiomers* in quantitative yields (eq 88).

The ortho-substituted benzene skeleton is found to be essential for this isomerization since non-benzofused 1,7-enynes did not provide six-membered prod-

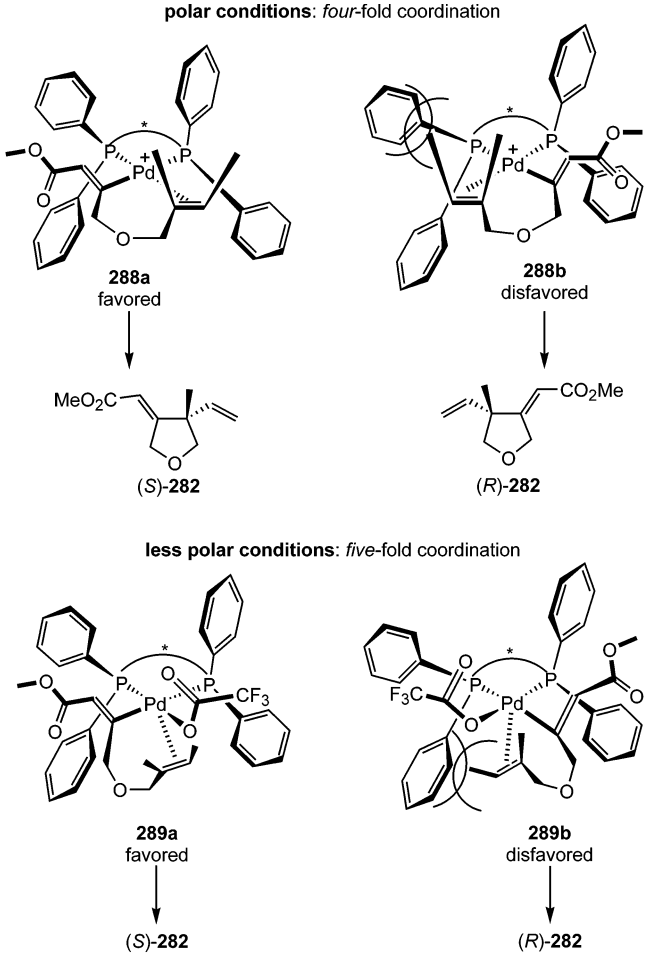
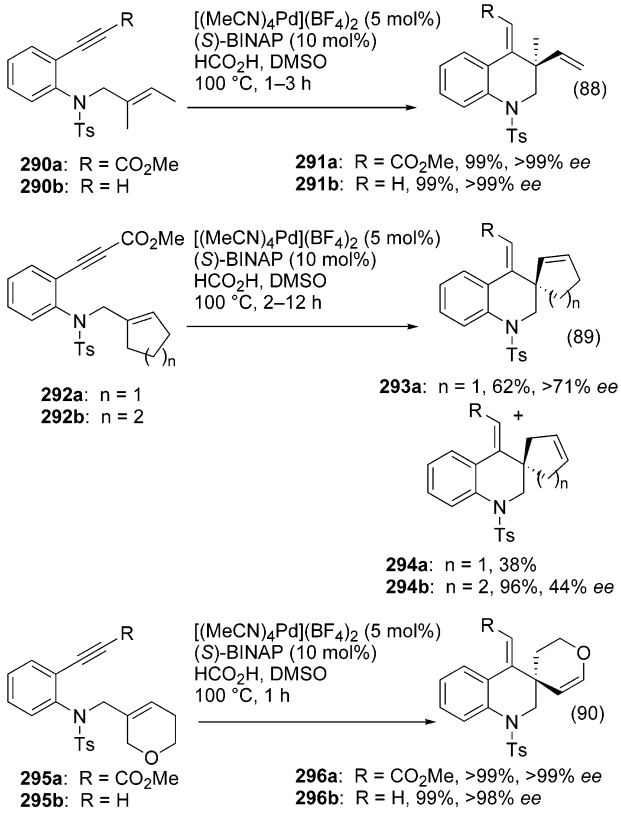
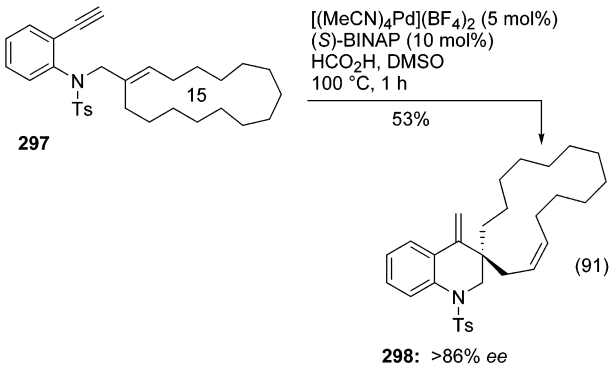


Figure 1. Transition states for the enantioselective carbocyclization catalyzed by chiral Pd^{II} complexes under polar or less-polar conditions.

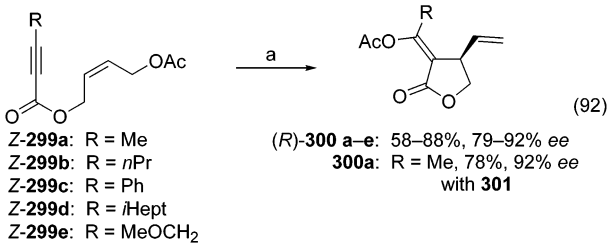


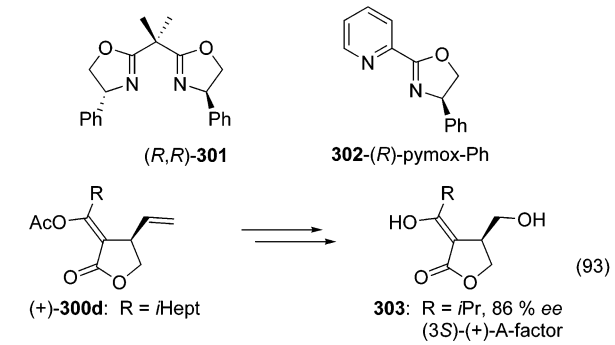
ucts. The enantioselective synthesis was also extended for the construction of spiro quinoline ring systems by cyclization of enyne substrates **292a**,**b** with a five- or six-membered olefin (eq 89). The enyne substrate **292a**, with a cyclopentene moiety, gave the desired product **293a** in 62% yield and 71% ee, along with the achiral olefin **294a** formed by migration of the double bond (38% yield). The enyne substrate **292b**, with a cyclohexene moiety, gave exclusively the double-bond-migrated spiro quinoline **294b** (96%) in 44% ee (eq 89). Interestingly, the transformation of substrates **295a**,**b** with a dihydropyran moiety (in which C−C double bond migration is not possible) proceeded successfully under these conditions to give the spiro ring products **296a**,**b** in quantitative yields and up to 99% ee (eq 90). Application of this novel spiro quinoline synthesis to substrate **297**, bearing a 15-membered cyclic olefin and a terminal acetylene, under previously described conditions yielded the double-bond-migrated macrocyclic spiro product **298** in moderate yield (53%) but with good enantioselectivity (86% ee) (eq 91).[113]



A mechanistically different, novel type of cyclization of the enyne esters **299**, initiated by acetoxypalladation to give acetoxymethylene γ-butyrolactones **300**, and its asymmetric catalytic version have been recently reported by Lu and co-workers (eq 92).[114] Using the phenyl-substituted bisoxazoline ligand **301** or (*R*)-pymox-Ph **302** in the presence of $Pd(OAc)_2$ in AcOH, the product lactones **300a**−**e** are formed in high yields, with ee's ranging between 79 and 92% (eq 92). The lactone **300d**, obtained in 86% ee, has been shown to be a useful intermediate for the synthesis of enantioenriched (3*S*)-(+)-A factor **303** (eq 93). A plausible mechanism involving a *trans*-acetoxypalladation of the triple bond, followed by an intramolecular olefin insertion and a subsequent deacetoxypalladation of the intermediate **305** to give **300**, has been suggested for this novel transformation (Scheme 7).

The authors have proposed tetrahedral models **305a** and **305b** for the transition-state intermediate, in which the steric interaction between the allylic ester and the proximal phenyl substituent of the (*R*,*R*)-oxazoline **301** would prefer the intermediate **305a** (with the Pd atom situated in front of the olefinic double bond) over **305b**, leading to the γ-butyrolactones **300** with 3-(*R*) configuration.[114b]

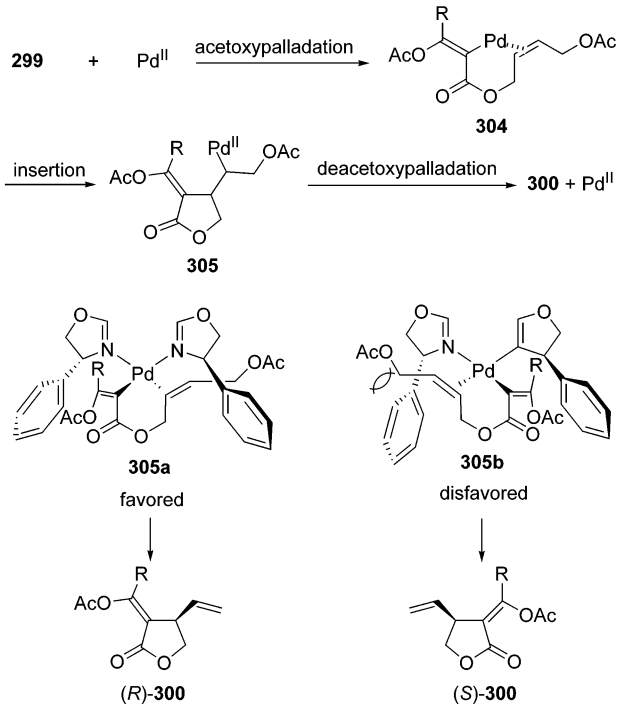


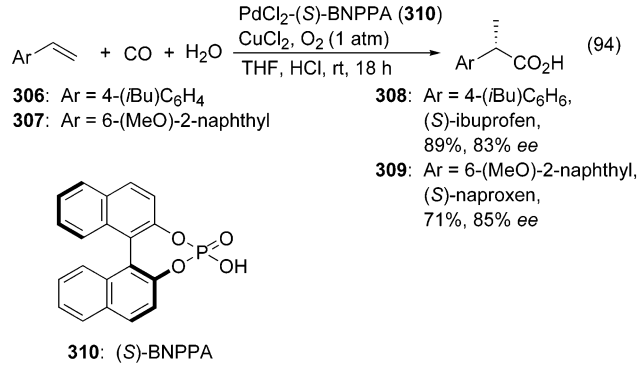


6. Carbonylation and Cyclocarbonylation Reactions

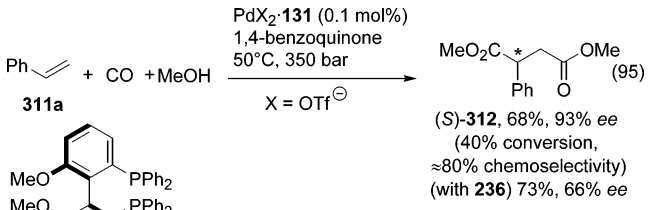
The palladium-catalyzed carbonylation of organic substrates is one of the most efficient methods of homologation, and the corresponding asymmetric hydroformylation, hydrocarboxylation, and hydroesterification of prochiral olefins (in particular vinylarenes) using Pd and other transition metals (Rh or Ni) have been actively investigated.[115] A potential application is the enantioselective synthesis of α-arylpropionic acids as anti-inflammatory agents. Thus, the two commercially important anti-inflammatory drugs, i.e., (*S*)-ibuprofen **308** and (*S*)-naproxen **309**, could be obtained in high chemical yields with good enantioselectivity and complete regioselectivity under exceptionally mild conditions by a Pd-catalyzed hydrocarboxylation of the corresponding 4-(isobutyl)-styrene **306** and 2-vinyl-6-methoxynaphthalene **307**, respectively. The commercially available (*S*)-1,1′-binaphthyl-2,2′-dihydrogen phosphate (BNPPA) **310** was used as ligand (eq 94).[116] The reaction appears to be one of the most industrially attractive syntheses in this field.

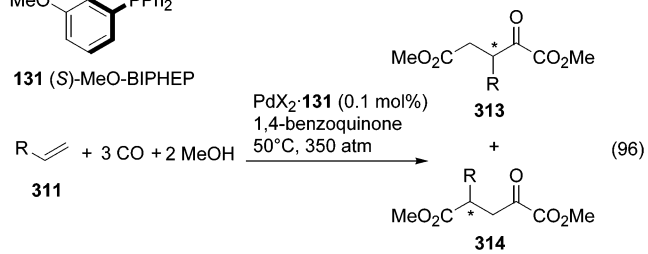
Scheme 7. Plausible Mechanism for Pd-Catalyzed Cycloisomerization of Enyne 299 to 300 (Eq 92)





Similarly, Consiglio and co-workers reported an enantioselective bisalkoxycarbonylation of 1-alkenes for the synthesis of optically active butanedioic acid derivatives, which are important building blocks in the synthesis of pharmaceuticals.[117] Using cationic palladium(II) complexes of type $Pd(L{-}L^1)(S_2)X_2$ (S = solvent, X = OTf) with atropisomeric chiral ligands such as (*S*)-MeO-BIPHEP (**131**), the corresponding phenylsuccinate (*S*)-**312** is formed along with oligomers with high chemo- (~80%) and enantioselectivity (93%) when styrene is the substrate (eq 95).





entry	R	tot. conv. [%]	yield[a] [%]	regioselectivity 313/314	ee [%]
1	Ph (**311a**)	80	25	100/0	92
2	Me (**311b**)	60	5	36/64	59/61
3	*i*Bu (**311c**)	13	17	50/50	81/62
4	Bn (**311d**)	5	8	54/46	78/30

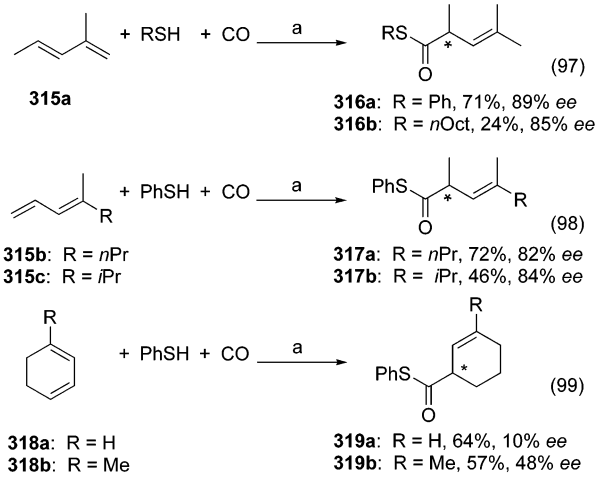
[a] mole of oxoglutarates / mole of converted substrate

In contrast, low yields and modest to low ee's have been observed when aliphatic alkenes such as propene and 4-methyl-1-pentene are used for the bisalkoxycarbonylation, probably due to two competing regiochemical pathways for the insertion of the olefin into the palladium carbomethoxy intermediate. Re-

cently, chiral bisoxazoline (**236**)[118] and phosphane sulfide[119] ligands have also been examined in this reaction employing styrene and other olefins, yielding the butanedioates in modest yields and low ee's (8−66%).

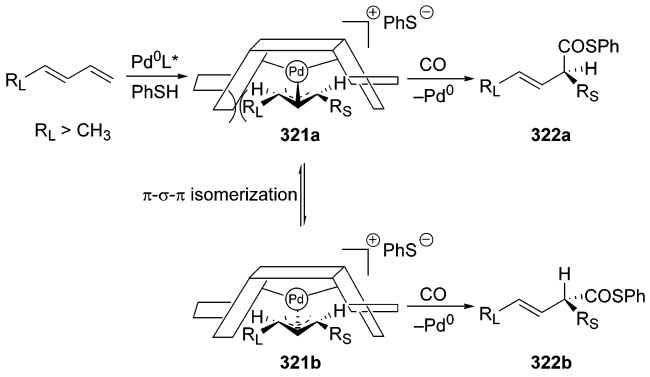
Consiglio et al. also developed an enantioselective triple carbonylation of olefins, catalyzed by a similar cationic palladium complex in the presence of (*S*)-MeO-BIPHEP **131**, to give the regioisomeric 2-oxoglutarates **313** and **314** in varying yields and ee's (eq 96).[120] The reaction is found to be completely regioselective for styrene (entry 1), whereas with aliphatic olefins, both regioisomers are formed (entries 2−4). Even though the yield is not high, the reaction allows a one-step synthesis of substituted 3-oxoglutarates with fair to excellent enantioselectivity (ee up to 92%, entry 1).

Alper and co-workers have recently reported the first example of an enantioselective thiocarbonylation involving a three-component reaction of prochiral 1,3-dienes with thiols and carbon monoxide, catalyzed by palladium complexes with (*R*,*R*)-DIOP (**320**) as ligand, to produce enantioenriched β,γ-unsaturated thio testers (eqs 97−99).[121] This thiocarbonylation



reaction is highly regioselective and, depending on the structural characteristics of the substrates, 1,4- or 1,2-addition products are obtained. Thus, reaction of 2-methyl-1,3-pentadiene **315a** with either thiophenol or aliphatic thiol and CO under optimal conditions afforded, in a 1,4-addition, the β,γ-unsaturated thio esters **316a**,**b** in 71 and 24% yield, respectively with high ee's (85−89%) (eq 97). In contrast, the bulkier dienes **315b**,**c** gave the unsaturated thio esters **317a**,**b** by a 1,2-addition with high ee's (eq 98). On the other hand, asymmetric thiocarbonylation of cyclic 1,3-dienes **318a**,**b** with formation of **319a**,**b** gave poor results with low to modest ee's (10−48%) (eq 99) that could not be improved by

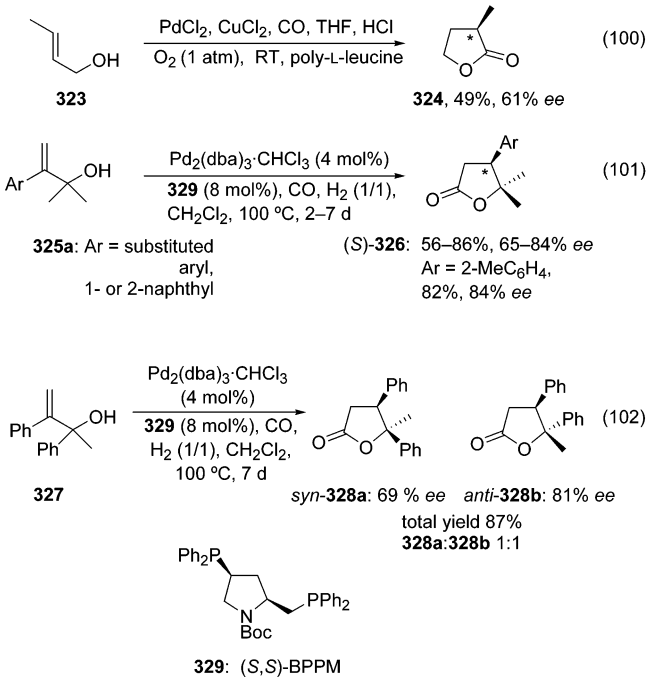
Scheme 8. Predicted Path for the Asymmetric Thiocarbonylation Using (*R*,*R*)-DIOP (Eqs 97−99)



changing the chiral ligand.[121] The authors have proposed **321a** and **321b** as transition-state models, which are derived from ground-state structures of the ligand−palladium−π-allyl complex and Trost's hypothesis regarding the structural features required for creating chiral space. Molecular modeling indicates that the energy difference between **321a** and **321b** is approximately 2.37 kcal/mol. The enantiodifferentiation step in this asymmetric thiocarbonylation is presumed to be the CO insertion into either **321a** or **321b**, which can result in the formation of either **322a** or **322b**, respectively. The transition-state energy for the CO insertion into **321b** is lower than that for the CO insertion into **321a** due to the smaller steric interaction between the "wall" and the substituent R_L. Thus, the reaction via **321b** is faster and gives **322b** as the major enantiomer (Scheme 8).

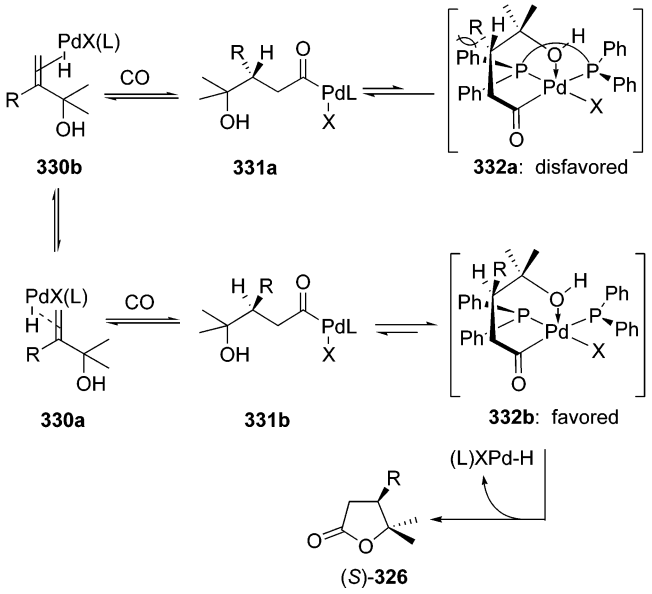
Palladium-catalyzed cyclocarbonylation with carbon monooxide has been extensively investigated by Negishi[122] and Alper,[123] and the reaction represents a useful method for the synthesis of cyclic ketones, lactones, and lactams. However, to our knowledge, only a few applications of this useful reaction using chiral Pd catalyst have been described so far. Alper and co-workers have investigated the Pd-catalyzed cyclocarbonylation of allylic alcohols[123] and developed the first enantioselective variant of this reaction for the synthesis of chiral γ-butyrolactones,[124] which is an important functionality in several natural products. In earlier studies,[125] cyclocarbonylation of unsaturated alcohols such as **323** in the presence of a chiral ligand based on poly-L-leucine was reported to give the optically active lactone **324** in only 61% ee (eq 100).

Recently, phosphane ligands such as (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-pyrrolidine **329**, with a 1:1 mixture of CO and H_2, were shown to afford the aryllactones **326** from the unsaturated aryl alcohols **325** in 65−84% ee. After recrystallization, the product **326** could be obtained in >99% optical purity (eq 101).[123a,126] Furthermore, the corresponding *syn*- and *anti*-lactones **328a** and **328b** were formed in 69 and 81% ee from the racemic **327** without any diastereomeric bias under similar conditions using chiral ligand **329** (eq 102).[124,126] A probable mechanism involving the diastereomeric acylpalladium complexes **331a** and **331b**, formed by the initial coordi-



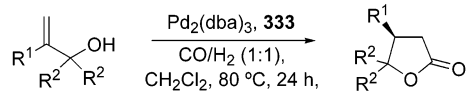
nation−addition of the palladium hydride species to allylic alcohol, followed by insertion of CO, has been postulated (Scheme 9).

Scheme 9. Proposed Mechanism for Enantioselection in the Pd-Catalyzed Cyclocarbonylation of Allylic Alcohols

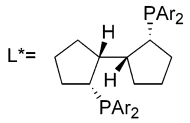


It has been suggested that the intramolecular cyclization involving coordination of the OH group to the Pd center in intermediate **331** appears to be responsible for the enantioselection. The formation of the coordinated complex **332a** from **331a** is expected to be disfavored because of the steric interaction between the group R and the phenyl ring which is absent in the cyclization of **331b** to **332b**, thus forming lactone (*S*)-**326** (R = Ar, Scheme 9).

Zhang and co-workers[127a] have reported a highly enantioselective cyclocarbonylation of substituted *β*-allylic alcohols catalyzed by a Pd complex with chiral BICP ligands **333** (eqs 103−105), which significantly enhances the scope and synthetic utility of this cyclocarbonylation reaction. High yields and ee's were obtained with xyl-BICP ligand **333b** in the cyclocarbonylation of **325a** (R^1 = Ph, R^2 = Me) to give **326a** in 87% yield and 95% ee, which is the highest ee reported to date for this compound (eq 103).

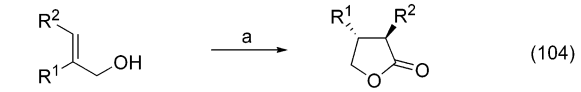


	R^1	R^2	L*	yield **326** [%]	*ee* [%]
325a	Ph	Me	**333b**	87	95
325b	4-FC_6H_4	Me	**333b**	91	96
325c	2-MeC_6H_4	Me	**333b**	91	92
325d	1-naphthyl	Me	**333a**	90	91
325e	Me	Me	**333a**	95	49
325f	Me	Ph	**333b**	91	74



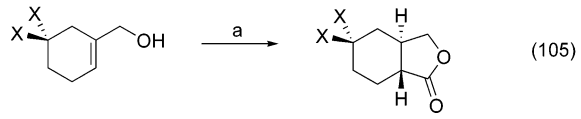
333a: BICP, Ar = Ph
333b: xyl-BICP, Ar = 3,5-$Me_2C_6H_3$

The asymmetric cyclocarbonylation studies were also extended to *β*,*γ*-disubstituted allylic alcohols **334** without geminal dialkyl substituents at the α-position, yielding *trans*-α,*β*-disubstituted chiral lactones **335**, which are key structural features of thebiologically important lignans (eq 104).



334a: R^1= Me, R^2= Ph
334b: R^1= R^2= Ph
334c: R^1= Ph, R^2= Et
334d: R^1= R^2= Me

335a: 54%, 84% *ee*
335b: 60%, 93% *ee*
335c: 39%, 93% *ee*
335d: 89%, 45% *ee*



336a: X = H
336b: X = -O-$(CH_2)_2$-O-

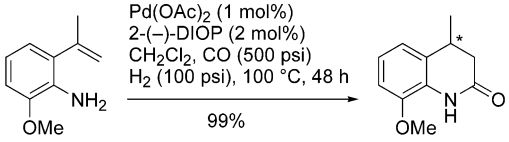
337a: 87%, 93% *ee* (*R*,*R*)
337b: 97%, 86% *ee* (*R*,*R*)

a) $Pd(OAc)_2$, **333a**, $ClCH_2CH_2Cl$, 80 °C, 24 h, CO, H_2 (1/1), 800 psi

Thus, the differently substituted allylic alcohols **334a**−**d** could be cyclized to afford the *γ*-butyrolactones **335a**−**d** with either **333a** or **333b** as chiral ligands in good to excellent yields and high ee's varying between 84 and 93% (except for **335d**). A notable advance emerging from these studies is the asymmetric cyclocarbonylation of the six-membered cyclic allylic alcohols **336a**,**b** using Pd−BICP catalyst **333a**, which yielded the bicyclic butyrolactones **337a**,**b** in high ee's up to 93% with good yields (eq 105). The

chiral butyrolactone **337b** is a key intermediate in Weinreb's recent synthesis of the antitumor agent papuamine.[127b,c]

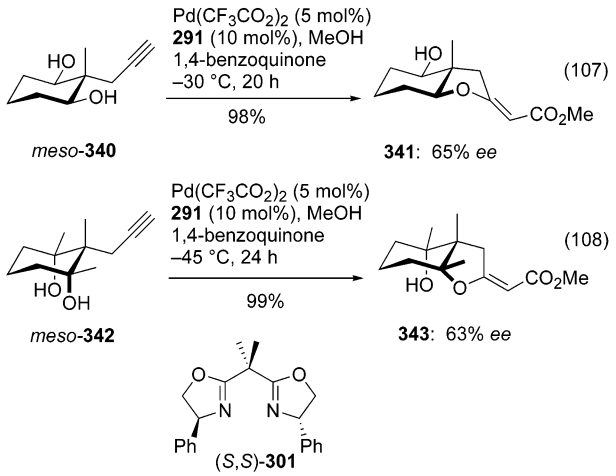
In a similar way, lactams can also be formed. Thus, a palladium-catalyzed cyclocarbonylation of 2-(1-methylvinyl)anilines to give lactams has been investigated by Alper and co-workers.[128] The use of $PdOAc_2$−(−)-DIOP catalyst gave a maximum ee of 54% for the 3,4-dihydro-4-methyl-2-(1*H*)-quinolin-2-one (**339**) from *o*-vinylaniline **338** (eq 106).



(106)

338 **339**: 54% *ee*

The first example of a palladium(II)-catalyzed asymmetric cyclization−carbonylation of cyclic *meso*-2-methyl-2-propargyl-1,3-diols **340** and **342** in the presence of chiral bisoxazoline (*S*,*S*)-**301** to afford (*E*)-bicyclic *β*-alkoxyacrylates **341** and **343**, respectively, in high yields and moderate enantioselectivity (63−65%) has been recently reported by Kato and co-workers (eqs 107 and 108).[129]



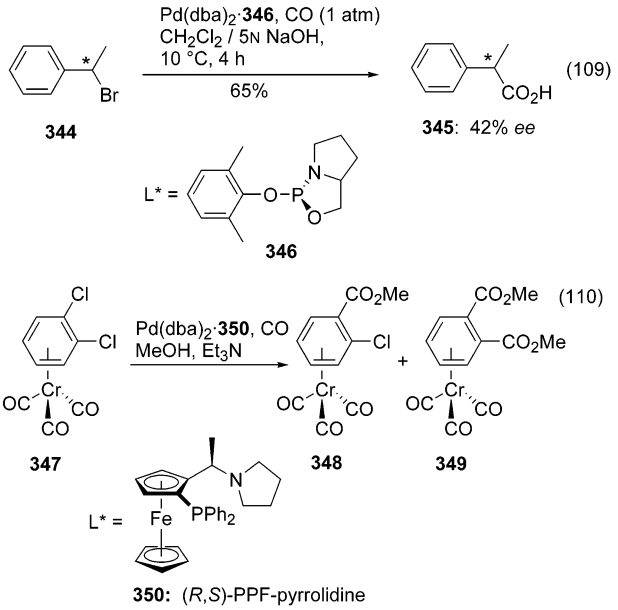
(107)

(108)

Another recently described Pd^{II}-catalyzed enantioselective reaction is the benzoylation of racemic secondary alcohols.[130] In this transformation, a kinetic resolution was observed during carbonylative acylation with carbon monoxide and an organobismuth(V) compound, i.e., $Ph_3Bi(OAc)_2$, in the presence of the chiral oxazolinylferrocenylphosphine ligand **124a** to give benzoylated alcohols, though with low ee's.

An asymmetric palladium-catalyzed carbonylation of aliphatic bromides has been reported by Arzoumanian[131] under phase-transfer conditions (eq 109). Thus, Pd-catalyzed carbonylation of the racemic α-methylbenzyl bromide **344** in the presence of Pd(dba)$_2$ and chiral 2-substituted 3,1,2-oxaphosphalane **346** in the presence of NaOH resulted in formation of 2-phenylpropionic acid **345** in 65% yield and a modest ee of 42%.

Recently, Schmalz and co-workers have reported[132] on a catalytic enantioselective entry to planar chiral *π*-complex **348** by palladium-catalyzed monomethoxy-



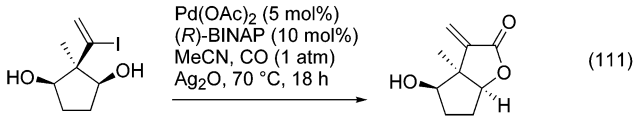
(109)

(110)

entry	cat. [mol%]	time [h]	yield **348** [%]	yield **349** [%]	*ee* **348** [%]
1	5	1	47	23	63 (1*S*)
2	5	1.5	38	50	92 (1*S*)
3	10	0.5	48	21	64 (1*S*)
4	2	3	31	48	95 (1*S*)

carbonylation of 1,2-dichlorobenzene tricarbonylchromium(0) **347** in the presence of the chiral ferrocene ligand (*R*,*S*)-PPF-pyrrolidine **350** with enantiomeric excess up to 95% (eq 110). With this ligand, a significant dependency of enantioselectivity on the reaction time (conversion) was observed (entry 1 vs entry 2), whereas no significant influence on enantioselectivity was found upon increasing the amount of catalyst (entry 3). With only 2 mol % of the catalyst, the product **348** is obtained in 95% ee (31% yield) after 3 h, together with formation of a 48% yield of the of bis(methoxy) product **349** (entry 4). This increase in enantioselectivity of **348** with time has been explained by subsequent kinetic resolution connected to the formation of bis(methoxy) product **349** (eq 110).[132]

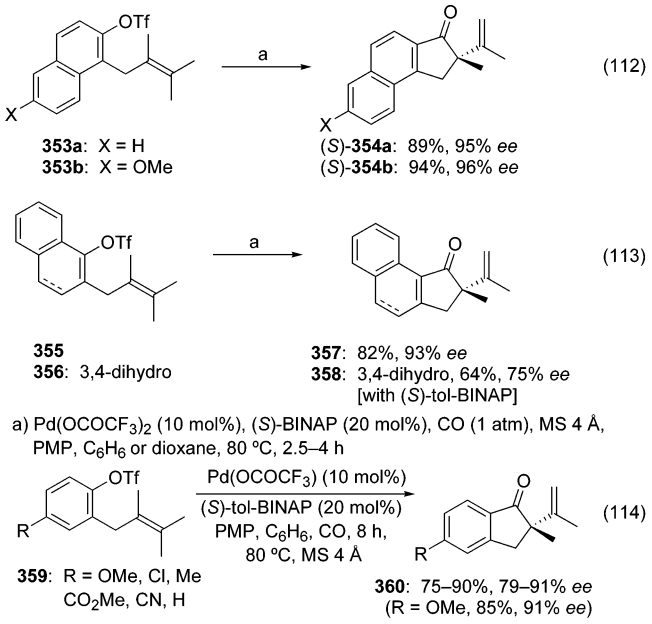
A catalytic enantioselective synthesis of α-methylenelactones by cyclocarbonylation of prochiral alkenyl halides **351** has been developed by Shibasaki and co-workers (eq 111).[133] Using a combination of



(111)

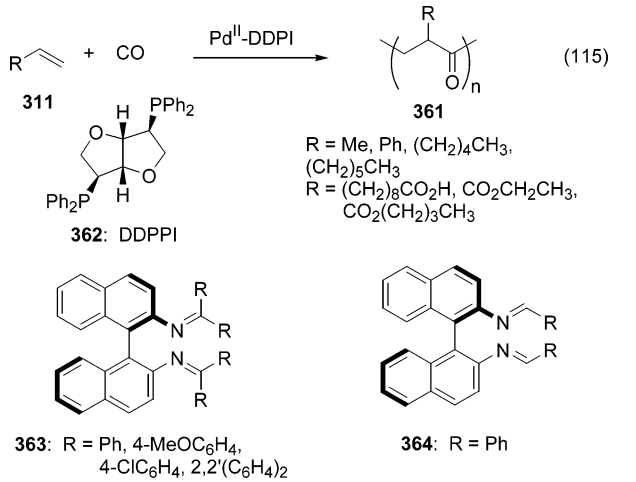
$Pd(OAc)_2$, (*R*)-BINAP, and Ag_2O gave the lactone **352** in 44% yield and modest ee (57%). In the absence of Ag_2O, no asymmetric induction was observed.

A recent report by Hayashi and co-workers[134] has described the asymmetric cyclocarbonylation of *o*-allylaryl triflates to afford enantioenriched indanones and their condensed derivatives, bearing a chiral quaternary center, with high yield and excellent enantioselectivity (eqs 112−114). Under optimal



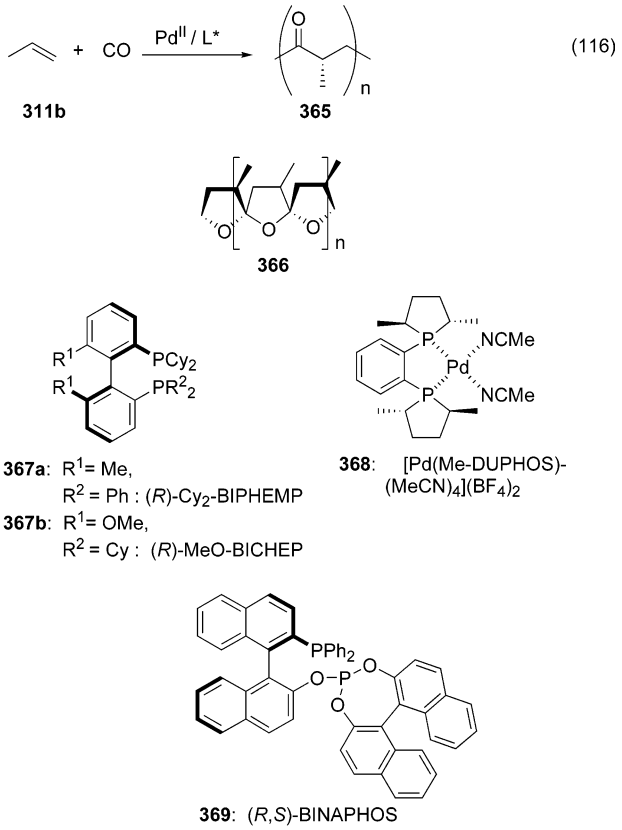
conditions using $Pd(CF_3CO_2)_2$ in the presence of chiral (*S*)-BINAP, PMP, and 4-Å molecular sieves, the naphthoindanone **354a** could be obtained from **353a** in 89% yield and 95% ee. Even better results were obtained in the transformation of **353b** to give **354b** (eq 112). The dihydronaphthaline **356** showed a lower selectivity compared to the naphthaline derivative **355** (eq 113). Of interest were also the reactions of the *o*-allylphenyl triflates **359** to afford **360**. Compared to the parent compound, the introduction of a substituent in the para position in **359** led to an increase in enantioselectivity, regardless of the electron-withdrawing or -donating characteristics (eq 114). The efficiency of this carbonylative cyclization was significantly improved by using the (*S*)-tol-BINAP/C_6H_6 system instead of (*S*)-BINAP/dioxane.

Lu and co-workers have used a palladium catalyst modified by a 1,4,3,6-dianhydro-2,5-dideoxy-2,5-bis-(diphenylphosphino)-l-iditol (DDPPI, **362**) for the enantioselective copolymerization of α-olefins such as propene, heptene, 1-octene, and styrene as well as functionalized olefins such as *ω*-undecylenic acid, ethyl acrylate, and butyl acrylate (eq 115).[135]



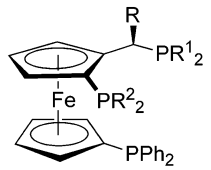
In a recent paper, Reetz and co-workers have reported the preparation of a new class of chiral ligands derived from C_2-symmetric chiral diketimines **363** and used them in Pd-catalyzed alternating copolymerizations of 4-*tert*-butylstyrene with carbon monoxide.[136] Thus, under optimized conditions, activities of up to 110 kg of polymer per mole of Pd could be achieved applying $[ketimine/PdCH_3]^+BARF^-$ to yield polymers with an isotacticity of >97%. On the other hand, the Pd catalysts derived from chiral C_2-symmetric dialdimines **364** were found to be inactive in this copolymerization reaction. Furthermore, these workers have developed a theoretical AMS model (Accessible Molecular Surface) to rationalize the observed extreme differences in catalytic activity within the diketimine and dialdimine series.

Palladium-catalyzed enantioselective alternating copolymerization of α-olefins with carbon monoxide is an attractive methodology to obtain optically active polymers containing carbonyl groups which are capable of further functionalization.[137] Consiglio and co-workers reported the first successful example of an asymmetric copolymerization of propene with CO (eq 116) by use of the chiral electron-rich biphosphine ligand (*R*)-Cy_2-BIPHEMP (or (*S*)-BICHEP) **367** with high isotacticity.[7d,138]



Similarly, completely isotactic alternating copolymerization of propene−CO was achieved by Sen and co-workers[7c,139] using chiral bis(dialkylmonoarylphosphine) Me-DUPHOS (**368**) and by Takaya and Nozaki[7a,140] in 1995 employing unsymmetrical phosphane-phosphite BINAPHOS ligands such as (*R*,*S*)-BINAPHOS **369**. The copolymer has a *γ*-polyketone structure **365** in solution [$CHCl_3$ or $(CF_3)_2CHOH$],

Table 10. Influence of Some Ferrocenyl Ligands 375 in Copolymerization of Propene with Carbon Monooxide (Eq 116)[a]

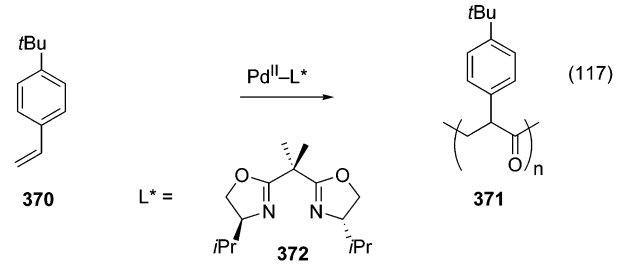


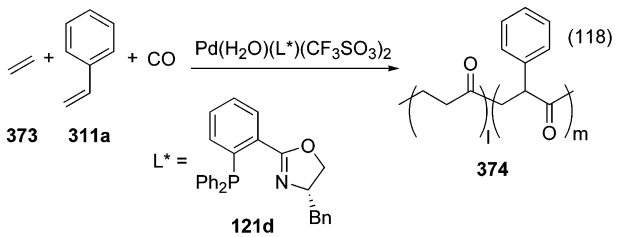
375a-l: (*R*)(*S*$_P$)JOSIPHOS

entry	L*	R	R^1	R^2	% regio-regularity (h−t)	% stereo-regularity	productivity (g·g(Pd)$^{-1}$·h^{-1})
1	**375a**[b]	Me	Cy	Ph	99	91	165
2	**375b**[b]	Me	Et	Ph	98	74	88
3	**375c**[c]	Me	Ph	Cy	98	78	28
4	**375d**[c]	Me	Cy	Cy	100	91	35
5	**375e**[c]	Me	Ph	Ph	98	63	38
6	**375f**[b]	H	Cy	Ph	98	72	40

[a] $Pd(OAc)_2$, $Ni(ClO_4)_2 \cdot 6H_2O$, naphtho-1,4-quinone. [b] In THF/MeOH/$CH(OMe)_3$, 50 °C. [c] In THF/MeOH at 42 °C.

whereas in the solid state it partially forms the polyspiroacetal structure **366**. Brookhart and coworkers[7b,141] have reported the first example of an asymmetric copolymerization of styrene (eq 117) with high enantiopurity and complete isotacticity using bisoxazoline ligand **372**. A successful enantioselective terpolymerization of styrene, ethene, and CO has also been achieved recently by employing a catalytic system with a Pd−phosphineimine (**121d**) (eq 118).[142]





A highly efficient Pd^{II} catalyst system, modified by applying (*R*)-(*Sp*)-1-[2-(diphenylphosphanyl)ferrocenyl]-ethyldicyclohexylphosphane **375** (JOSIPHOS), has been reported by Consiglio and Togni[143] (productivity of up to 600 g·g[Pd]$^{-1}$·h^{-1} for the regioregular isotactic specific copolymerization of propene with CO. With this system, both a very high regioregularity (>99%, head-to-tail enchainment) and stereoregularity (>96% of isotactic diads) were achieved. A study of the related ligands **375a**−**f** (Table 10) shows that the presence of a stereogenic center in addition to the planar chirality in **375** (R = Me) is essential to achieve good stereochemical control, since the ligand **375f** (R = H) exhibited diminished stereoregularity in comparison to **375a** (Table 10, entry 6 versus entry 1).

Also the presence of the bulky dialkylphosphino group at the stereogenic center is important to achieve good stereocontrol (Table 10, **375a** versus **375b**). The best results for catalytic activity and stereoselectivity were obtained with ligands having larger differences between the electronic characteristics of the two phosphorus atoms (a basic PCy_2 and a slightly acidic PPh_2 donor in the ligand **375a**). In a recent paper, Consiglio and Togni[144] have further investigated the role of electronic differentiation of the two binding sites in these ligands **375** and shown that the Pd^{II} system, combined with sterically very similar chiral ferrocenyl ligands (**375a** and **375g**−**l**, except **375j**), efficiently catalyzed the completely isotactic copolymerization of propene and CO in a highly enantioselective fashion. By changing the electronic properties of the PAr_2 substituent, only a small variation in enantiofacial discrimination was observed, whereas drastic changes in catalytic activity were noted (Table 11).[144]

7. Cycloaddition Reactions

7.1. Diels−Alder Reactions

The asymmetric Diels−Alder reaction is one of the most powerful and versatile reactions in organic synthesis, and catalytic enantioselective processes with chiral Lewis acids have significantly extended the scope and utility of this reaction.[145] Oi and coworkers[146] have shown for the first time the use of Pd^{II} cationic complexes for the Diels−Alder cycloaddition of α,β-unsaturated carbonyl compounds with dienes in both its achiral and enantioselective versions (eq 119). Thus, the reaction of *N*-acryloyloxazolidinone **376a** with cyclopentadiene in the presence of $[Pd(S\text{-BINAP})(PhCN)_2]X_2$ (X = BF_4) gave the adduct **378a** with high endo selectivity in 95% yield and 99% ee (Table 12, entry 1).

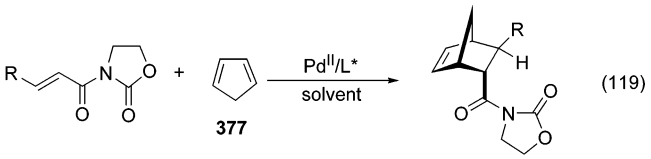
Table 11. Effect of Electronic Differentiation of the Two Binding Sites in Chiral Ligand 375 on CO/Propene Copolymerization (Eq 116)[a]

375	R	R^1	R^2	productivity (g·g(Pd)$^{-1}$·h^{-1}]	% regio-regularity	% stereo-regularity
375a	Me	Cy	Ph	369	>99	94−95
375g	Me	Cy	3-$(CF_3)C_6H_4$	1044	>99	97.5
375h	Me	Cy	4-$(CF_3)C_6H_4$	1160	>99	96.8
375i	Me	Cy	3,5-$(CF_3)_2C_6H_3$	1797	>99	97.5
375j	Me	Cy	2-$(CF_3)C_6H_4$			
375k	Me	Cy	3,5-$(MeO)_2C_6H_3$	50	99	90−92
375l	Me	Cy	3,5-$Me_2C_6H_3$	223	>99	93−94

[a] $Pd(OAc)_2$, **375**, $BF_3 \cdot Et_2O$, CH_2Cl_2/MeOH, 50 °C, 3 h.

Table 12. Pd-Catalyzed Enantioselective Diels–Alder Reaction of 376 with Cyclopentadiene (377) (Eq 119)

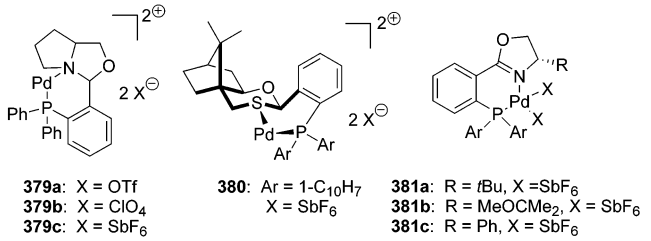
entry	376	Pd^{II} catalyst (mol %)/ reaction conditions	product	endo/ exo	endo product yield (%)	endo product ee (%)	ref
1	**376a**	[Pd(*S*-BINAP)(PhCN)$_2$](BF$_4$)$_2$ (10), CH_2Cl_2, −50 °C, 24 h	**378a**	95:5	95	99 (2*R*)	146
2	**376a**	[Pd(*R*-BINAP)(ClO$_4$)$_2$] (10), CH_2Cl_2, −78 °C, 24 h	**378a**	97:3	75	99 (2*S*)	147
3	**376a**	**379c** (10), CH_2Cl_2, −45 °C, 24 h	**378a**	97:3	96	98 (2*R*)	148
4	**376a**	**380** (5), CH_2Cl_2, −78 °C, 5 h	**378a**	91:9	92	93 (2*R*)	149
5	**376a**	**381a** (20), $EtNO_2$, −78 °C, 48 h	**378a**	97:3	76	99 (2*S*)	150
6	**376a**	**382** (20), CH_2Cl_2, −78 °C, 8 h	**378a**	95:5	89	72 (2*S*)	151
7	**376a**	**383a** (20), CH_2Cl_2, −78 °C, 8 h	**378a**	91:9	96	79 (2*S*)	151
8	**376a**	**384** (10), CH_2Cl_2, −60 °C	**378a**	95:5	95	75−	152
9	**376b**	**379c** (5), CH_2Cl_2, −35 °C, 36 h	**378b**	96:4	73	98 (2*R*)	148
10	**376b**	**381a** (20), CH_2Cl_2, −78 °C, 12 h	**378b**	91:9	81	71 (2*S*,3*R*)	150
11	**376c**	**381c** (20), CH_2Cl_2, −78 °C, 48 h	**378c**	89:11	73	69 (2*R*,3*S*)	150
12	**376d**	[Pd(*R*-BINAP)(ClO$_4$)$_2$] (10), CH_2Cl_2, −40 °C, 4 h	**378d**	72:23	91	57 (2*R*)	147
13	**376d**	**379c** (5), CH_2Cl_2, −45 °C, 24 h	**378d**	94:6	95	98 (2*S*)	148
14	**376d**	**380** (5), CH_2Cl_2, −78 °C, 92 h	**378d**	75:25	61	86 (2*S*)	149



376a: R = H
376b: R = Me
376c: R = Ph
376d: R = CO_2Et

378a: R = H
378b: R = Me
378c: R = Ph
378d: R = CO_2Et

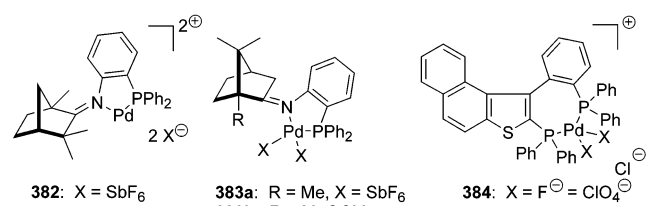
In an another report, Ghosh and co-workers[147] have investigated chiral Pd^{II} biphosphine complexes and their counterion effects in the asymmetric Diels–Alder reaction of cyclopentadiene with various *N*-acryloyl-oxazolidinones and have shown that the Pd–BINAP complex with a perchlorate counterion provides nearly complete endo diastereoselectivity and enantioselectivity with the 2*S* configuration of the cycloadduct **378a** (Table 12, entry 2). Recently, several groups have examined asymmetric Diels–Alder reactions catalyzed by cationic Pd^{II} complexes with a variety of chiral ligands, such as phosphinooxazolidine **379a**–**c**[148] and phosphinooxathiane **380**[149] by Nakano and Kuboto, phosphinophenyloxazolines **381a**–**c**[150] and chiral iminophosphines **382**, **383a**,**b**[151] by Hiroi, and 3-phenyl-2-(diphenylphosphino)naphtho[2,1-*b*]thiophene **384**[152] by Sannicolò and co-workers (Table 12). The chiral cationic Pd^{II}–phosphinooxazolidine complex **379c** with the hexafluoroantimonate counterion is shown to be highly effective with a wide range of *N*-acryloyl-oxazolidinone dienophiles, yielding adducts **378a**,**b** and **378d** in high yields and excellent ee's of 98% (Table 12, entries 3, 9, and 13).[148] The corresponding phosphinooxathiane–Pd^{II} complex **380** also allowed for the formation of the adducts **378a** and **378d** with good ee's (entries 4 and 14); however, it was less effective than **379c**.[149] An almost complete enantioselectivity was realized in the Diels–Alder reaction of **376a** catalyzed by the Pd^{II} complex **381a** with a diphenylphosphino *tert*-butyloxazoline (entry 5), whereas the reaction with crotonyl and cinnamyl derivatives **376b**,**c** gave products **378b**,**c** in lower ee's (entries 10 and 11).[150] The corresponding iminophosphine (**382**, **383a**)[151] and phosphinonaphtho[*b*]thiophene (**384**)[152] are found to be comparably less effective, with ee's of the adduct **378a** ranging between 72 and 79% (entries 6–8). Similarly, a significantly lower selectivity was observed for fumaroyl-oxazolidinone **376d** with the (*R*)-BINAP complex (entry 12), and the reaction with crotyl acid derivative **376b** was found to be very sluggish even at 23 °C under these conditions.[146] Only one example of a Diels–Alder reaction of 1,3-cyclohexadiene with acryloyloxazolidinone using an (*S*)-BINAP–Pd^{II} complex has been reported to afford the adduct **386** with 92% ee but in lower yield (eq 120).[146]



379a: X = OTf
379b: X = ClO_4
379c: X = SbF_6

380: Ar = 1-$C_{10}H_7$, X = SbF_6

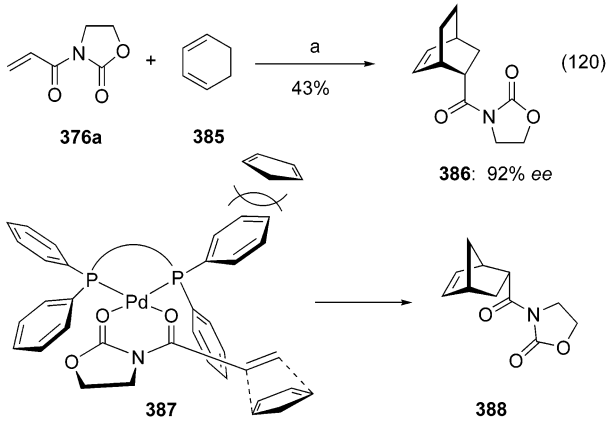
381a: R = *t*Bu, X = SbF_6
381b: R = $MeOCMe_2$, X = SbF_6
381c: R = Ph, X = SbF_6



382: X = SbF_6

383a: R = Me, X = SbF_6
383b: R = $MeOCMe_2$

384: X = $F^{\ominus}$ = $ClO_4^{\ominus}$



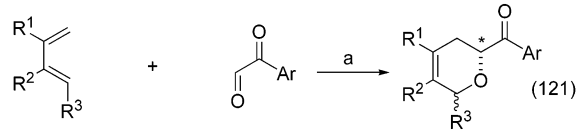
a) Pd(*S*-BINAP)(PhCN)$_2$(BF$_4$)$_2$ (10 mol%), CH_2Cl_2, 0 °C, 72 h

Recently, Strukul and co-workers have investigated the asymmetric Diels−Alder reaction of simple acroleins with cyclopentadiene in the presence of Pd^{II} catalyst modified with the (*R*)-BINAP ligand to yield the cycloadducts with low and moderate ee's (up to 49%).[153]

Various transition-state models with different chiral ligands have been proposed to rationalize high ee's in some of these reactions.[149−151] Thus, Oi and co-workers[146] have suggested a chiral induction model **387**, in which **376a** is coordinated with the chiral BINAP−Pd complex via the two carbonyl oxygen atoms. The attack of cyclopentadiene at the *endo-Si* face of the acryloyl group of **376a** in the square planar complex **387** is favored to afford the observed (2*R*)-adduct **378a**, while the attack at the *Re*-face may be obstructed by the equatorial phenyl group of (*S*)-BINAP.

7.2. Hetero-Diels−Alder Reactions

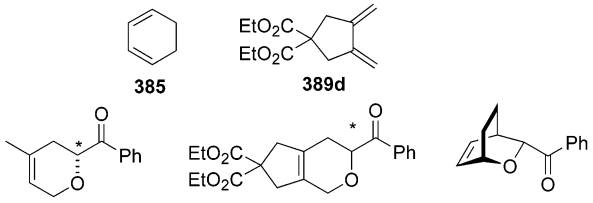
Oi and co-workers[154] first studied the enantioselective hetero-Diels−Alder cycloaddition[155] of nonactivated 1,3-butadienes with arylglyoxals and glyoxylates (eqs 121 and 122) using cationic BINAP−palladium and −platinum complexes as chiral catalysts.



(121)

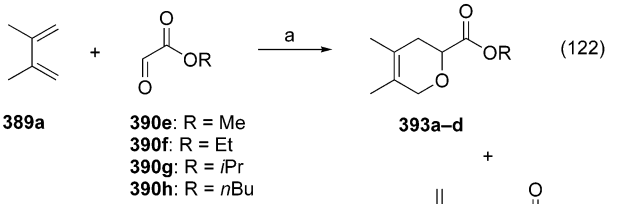
389a: R^1= R^2= Me, R^3= H **390a**: Ar = Ph **391aa–391da**
389b: R^1= CH_3, R^2= R^3= H **390b**: Ar = 4-$CH_3C_6H_4$
389c: R^1= R^3= CH_3, R^2= H **390c**: Ar = 4-$CH_3OC_6H_4$
390d: Ar = 4-ClC_6H_4

a) $Pd(S\text{-BINAP})(PhCN)_2(BF_4)_2$ (4 mol%), MS 3 Å, $CHCl_3$, 0 °C, 24 h
391aa–391da, R^1= R^2= Me, R^3= H, Ar = Ph, substituted aryl
50–70%, 94–99% *ee*, Ar = Ph, 70%, 99% *ee*, (*R*)



The cycloaddition of 2,3-dimethylbutadiene **389a** with phenylglyoxal **390a** in the presence of [Pd(*S*)-BINAP$(PhCN)_2$]$(BF_4)_2$ gave the cycloadduct **391aa** in 54% yield and with 79% ee, which was remarkably increased to 67% yield and 99% ee when the reaction was carried out in the presence of molecular sieves (3 Å MS). The transformation of **389a** with various substituted arylglyoxals **390b−d** under similar conditions with the same chiral catalyst also proceeded with high enantioselectivities to yield the products **391ab−391ad** in 50−70% yield and 94−99% ee (eq 121). However, the reaction of isoprene **389b** with **390a** gave the adduct **391ba** in lower yield (21%) as well as with low ee (33%). Similarly, with diene **389c**, also a cis−trans mixture of the products in low chemical and optical yields was obtained. On the other hand, the endo- and exocyclic dienes **385** and **389d** reacted smoothly with **390a**, furnishing the adducts **392** and **391da** in high yields and ee's (98−99%).

In contrast, the transformation of diene **389a** with glyoxylates, catalyzed by the cationic BINAP−Pd^{II} complex, gave in almost the same amount both the hetero-Diels−Alder product **393** and the ene product **394** (eq 122), with excellent ee's (95−97%) for the cycloadducts and moderate ee's for the ene products.



(122)

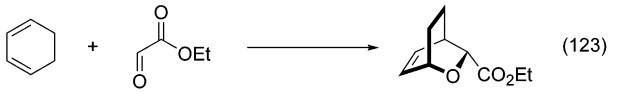
389a **390e**: R = Me **393a–d**
390f: R = Et
390g: R = *i*Pr
390h: R = *n*Bu

394: 32–35%, 57–76% *ee*

a) $[Pd(S\text{-BINAP})(PhCN)_2(BF_4)_2]$ (2 mol%), $CHCl_3$, MS 3 Å, rt, 20 h

product	R	yield [%]	*ee* [%]
393a	Me	34	95 (*R*)
393b	Et	36	95 (*R*)
393c	*i*Pr	43	97 (*R*)
393d	*n*Bu	42	96 (*R*)

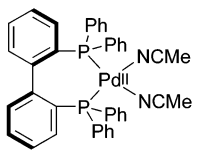
Similarly, the reaction of the cyclohexa-1,3-diene with ethyl glyoxylate afforded the endo adduct **395** selectively in good isolated yield (77%) with an excellent ee of 98% (eq 123, entry 1).



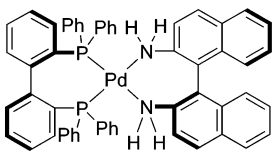
(123)

385 **390f** **395**

entry	Pd^{II} catalyst [mol%] reaction conditions	yield [%]	*ee* [%]
1	$[Pd(S\text{-BINAP})(PhCN)_2(BF_4)_2]_2$ $CHCl_3$, MS 3 Å, rt, 20 h	77	98
2	(*R*)-**396** (2), CH_2Cl_2, rt, 24 h	60	82
3	(*R*,*R*)-**397** (0.5), CH_2Cl_2, rt, 24 h	62	94
4	(*R*,*R*)-**397** (2), CH_2Cl_2, rt, 24 h	75	92



396: (*R*)-BIPHEP-Pd^{II}



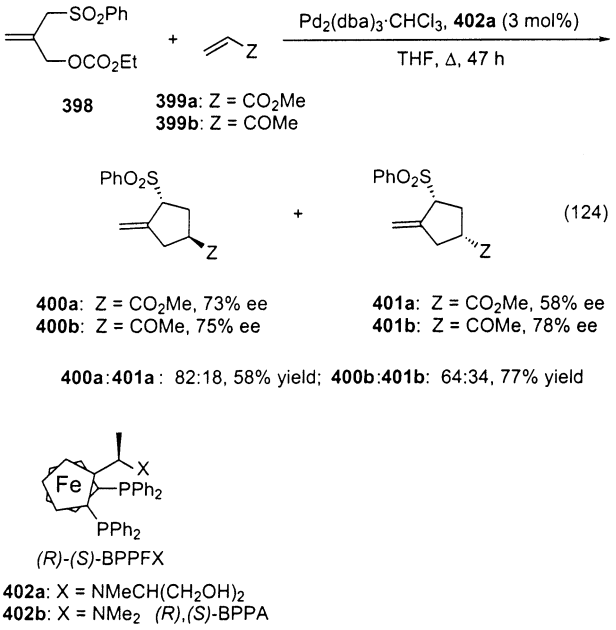
397: (*R*)-BIPHEP-Pd/(*R*)-DABN

A similar chiral induction model proposed earlier for Pd^{II}-catalyzed enantioselective Diels−Alder reactions with **387** as transition state has also been suggested for the observed enantioselectivity in these hetero-Diels−Alder reactions.[154] Recently, in an in-

teresting study Mikami and co-workers isolated enantiopure Pd complex **396** with a chirally flexible (*tropos*) biphenylphosphine (BIPHEP) ligand by resolution with enantiopure 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) at room temperature.[156a] Similarly, they also obtained enantio- and diastereomerically pure Pd complex **397** of *tropos*-BIPHEP through complexation of (*R*)-diaminobinaphthyl (DABN) with either enantiomer of the BIPHEP−Pd catalyst followed by *tropos*-inversion of the less favorable (*S*)-BIPHEP−Pd/(*R*)-DABN diastereomer to the more favorable (*R*)-BIPHEP−Pd/(*R*)-DABN diastereomer **397**.[156b] Both enantiopure *tropos*-BIPHEP complexes **396** and **397** are shown to catalyze hetero-Diels−Alder reactions efficiently at room temperature, yielding cycloadduct **395** with good to excellent yields and enantioselectivities (eq 123, entries 2−4).[156a,b]

7.3. [3+2] Dipolar Cycoadditions

The enantioselective [3+2] cycloaddition of ethyl 2-(benzenesulfonylmethyl)-2-propenyl carbonate **398** with methyl acrylate (**399a**) and methyl vinyl ketone (**399b**) in the presence of chiral Pd−ferrocenylphosphine catalysts **402a**,**b** has been reported by Hayashi and co-workers (eq 124).[157] The reactions yield *trans*-



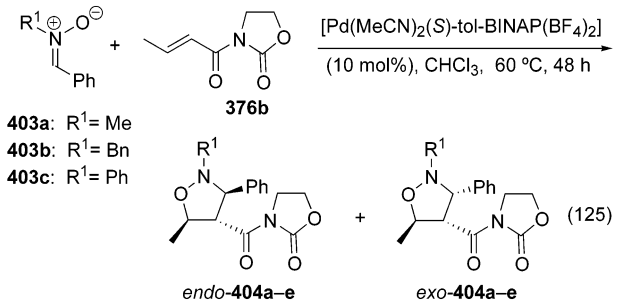
and *cis*-methylenecyclopentanes **400a**,**b** and **401a**,**b** in reasonably high ee's up to 78% using the chiral ligand **402a**.

Only a few catalytic asymmetric 1,3-dipolar cycloadditions using chiral Lewis acids have been reported so far.[158] However, these Lewis acid catalysts, which are quite moisture-sensitive, late transition metal Lewis acid complexes like those of palladium or ruthenium complexes, are often air stable and can be handled easily in the presence of water. The palladium-catalyzed asymmetric 1,3-dipolar cycloaddition between *N*-substituted *N*-benzylidenenitrones **403** and 3-alkenoyl-1,3-oxazolidin-2-one **376b** as dipolarophile has been successfully performed by Furukawa and co-workers,[159,160] yielding chiral isoxazolidine derivatives **404** in high yields with high enantioselectivities (eq 125).

Table 13. Enantioselective 1,3-Dipolar Cycloaddition of Nitrones 403 and Olefin 376b (Eq 125)

entry	nitrone	product	yield (%)	endo: exo	ee (%) endo	ee (%) exo
1	**403a**	**404a**	89	60:40	91	34
2	**403b**	**404b**	94	93:7	89	93
3	**403c**	**404c**	94	28:72	54	48
4	**403a**	**404a**	63	47:53	91	24

[a] Reaction with Pd^{II}−(*S*)-BINAP catalyst under identical conditions.



The catalyst system [Pd(MeCN)$_2${(*S*)-tol-BINAP}](BF$_4$)$_2$ gave better results than the corresponding (*S*)-BINAP analogue. Thus, the 2,5-dimethyl-3-phenylisoxazolidine derivative **404a** was obtained in 89% yield with 60% endo selectivity and with 91% ee (for the endo isomer **404a**) by the reaction of nitrone **403a** and 3-crotonyl-1,3-oxazolidin-2-one **376b** in the presence of the in situ-prepared Pd^{II}−(*S*)-tol-BINAP catalyst (Table 13, entry 1).[160] With the (*S*)-BINAP catalyst, a lower ee and lower endo/exo selectivity were observed, although the enantioselectivity of the endo isomer was identical (entry 4). On the other hand, in the reaction of the corresponding *N*-benzylnitrone **403b** and **376b**, the isoxazolidine **404b** (R′ = $PhCH_2$) was obtained in 94% yield (entry 2) with high endo selectivity (93:7) and with excellent enantioselectivities for both isomers. The reaction of *N*-phenylnitrone **403c** proceeded with high exo selectivity and with moderate enantioselectivity for both the exo and endo isomers (entry 3), whereas using the bulkier *N*-*tert*-butyl and *N*-trityl nitrones **403d** and **403e**, respectively, only traces of the isoxazolidine adducts **404d** (R = *t*-Bu) and **404e** (R = Tr) were formed. Furthermore, a transition-state model for the variation of endo/exo selectivity with *N*-substituent group on the nitrone **403** has been proposed.[160]

7.4. [3+2] Cycloadditions of Vinyloxiranes with Heterocumulenes

The palladium-catalyzed [3+2] cycloaddition reaction of oxiranes and aziridines with heterocumulenes is an efficient method to prepare five-membered heterocycles such as oxazolidine[161] and imidazolidine[162] derivatives. Recently, Alper and co-workers[163,164] have studied the catalytic asymmetric [3+2] cycloaddition of vinyloxiranes **405a** with heterocumulenes such as *N*,*N*-disubstituted symmetrical and unsymmetrical carbodiimides, yielding 4-vinyl-1,3-

Table 14. Pd-Catalyzed Enantioselective Cycloaddition of Vinyloxirane 405a with Unsymmetrical Carbodiimides (Eq 128)

entry	**411**	R^1	R^2	time	ratio **412**:**413**	yield [**412** + **413**] (%)	ee **412** (%)
1	**411a**	Ph	Cy	15 h	4:1	94	>99[a] (*R*)
2	**411b**	Ph	*t*Bu	4 d	9:1	58	>99[a] (*R*)
3	**411c**	4-ClC_6H_4	*n*Bu	15 h	1:1	96	93[b] (*S*)
4	**411d**	4-FC_6H_4	Cy	15 h	2:1	87	>99[b] (*S*) 97[a] (*R*)
5	**411e**	2,6-$Me_2C_6H_3$	Cy	36 h	3.5:1	55	88[a] (*R*)
6	**411f**	2,6-$Me_2C_6H_3$	*n*Bu	36 h	4:1	69	94[a] (*R*)

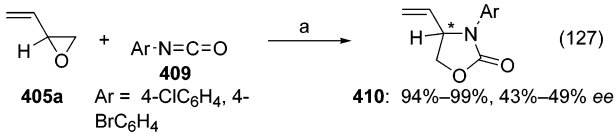
[a] With (*S*)-tol-BINAP. [b] With (*R*)-tol-BINAP.

oxazolidin-2-imines in high yields and enantioselectivity (eqs 126−128).

405a: R = H **406a–g** **407a–g**: R = H
405b: R = Me **408a–b, d**: R = Me

382	**383**	L*	R^1	product	%yield (% *ee*)
405a	**406a**	A	Ph	**407a**	98 (93)
405a	**406b**	A	4-ClC_6H_4	**407b**	95 (94)
405a	**406c**	A	4-MeC_6H_4	**407c**	98 (93)
405a	**406d**	A	4-BrC_6H_4	**407d**	84 (94)
405a	**406e**	A	4-$MeOC_6H_4$	**407e**	88 (88)
405a	**406f**	B	2-MeC_6H_4	**407f**	98 (88)
405a	**406g**	B	1-naphthyl	**407g**	60 (89)
405b	**406a**	B	Ph	**408a**	87 (91)
405b	**406b**	A	4-ClC_6H_4	**408b**	98 (69)
405b	**406d**	A	4-BrC_6H_4	**408d**	63 (84)[a]

A, (*S*)-tol-BINAP; B, (*R*)-tol-BINAP, [a] reaction time 3 d

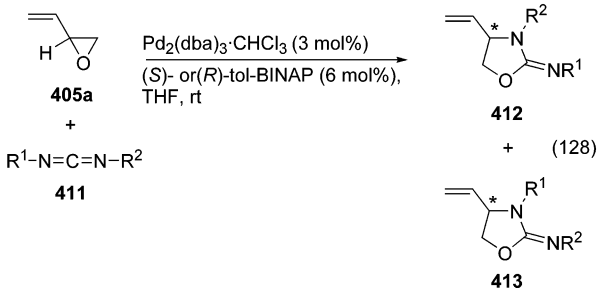


405a Ar = 4-ClC_6H_4, 4-BrC_6H_4 **410**: 94%–99%, 43%–49% *ee*

a) $Pd_2(dba)_3$·$CHCl_3$ (3 mol%), (*S*)-or(*R*)-tol-BINAP (6 mol%), THF, 15 h, rt

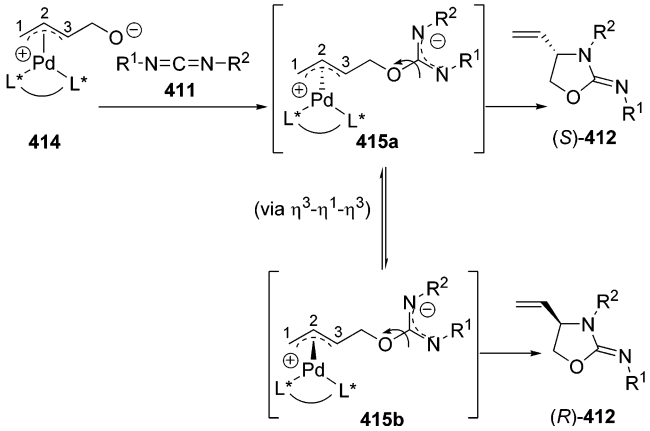
A study employing various commercially available chiral ligands gave the best chemical yields and highest enantioselectivity using (*R*)- and (*S*)-tol-BINAP ligands **8c** and *ent*-**8c**. A series of enantioenriched substituted 4-vinyl-1,3-oxazolidin-2-imines **407a**−**g** was synthesized by reacting vinyloxirane **405a** with the symmetrical *N*,*N*-diarylcarbodiimides **406** in the presence of $Pd_2(dba)_3$−(*S*)-tol-BINAP in yields of 60−98% and high ee's ranging between 88 and 94% (eq 126).[163] The 2-methyl-2-vinyloxirane **405b** reacted with diimides **406** more slowly and provided products in somewhat lower ee's (69−91%) compared to **405a**. On the other hand, the reaction of **405a** with isocyanates gave the corresponding 1,3-oxazolidin-2-ones **410** with much lower ee's (eq 127) compared to the transformation with the diimides **406**, although in comparably high chemical yields.[163] In a subsequent paper, Alper and co-workers extended these asymmetric cycloaddition studies to unsymmetrical diimides **411** (eq 128), yielding two isomeric products **412** and **413** in varying yields (Table 14).[164]

The presence of a bulky alkyl group (R^2 = cyclohexyl or *tert*-butyl) on one of the nitrogen atoms of

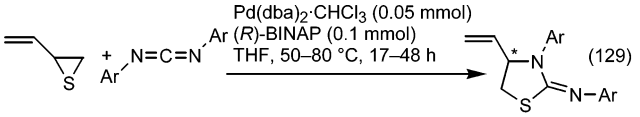


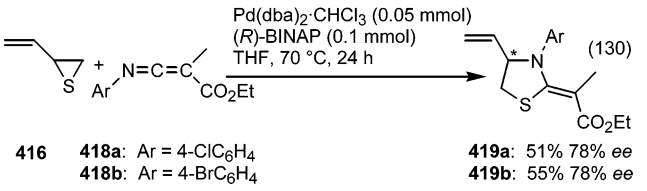
the carbodiimide enhanced the product ratio in favor of the *N*-aryl-3-alkyl-1,3-oxazolidin-2-imine **412** (R^2 = alkyl). Impressive results with high enantioselection were realized in these cycloadditions using Pd^0−tol-BINAP (Table 14). Reaction of **405a** with **411a** and **411d**, respectively, containing a cyclohexyl and a phenyl or a 4-fluorophenyl group gave **412a** and **413a** as well as **412d** and **413d**, respectively, in excellent enantioselectivities (entries 1 and 4, >99% ee for **412a** and **412d**); comparable results were obtained with **411b** containing a *tert*-butyl and a phenyl group (entry 2, >99% ee for **412b**). In contrast, lower enantioselectivities were obtained for entries 3 (93% ee for **412c**), 5 (88% ee for **412e**), and 6 (94% ee for **412f**). The high degree of asymmetric induction observed in these cycloadditions is explained by the pathway shown in Scheme 10. Oxidative addition of vinyloxirane **405** to the Pd^0 species, followed by the reaction of the (π-allyl)palladium intermediate with the heterocumulene, generates the diastereomeric zwitterionic palladium intermediates **415a**,**b**. The stereodeterminating step in this reaction appears to be the intramolecular nucleophilic anion capture by the nitrogen nucleophile at C-3 of the (π-allyl)palladium intermediate **415**. It has been suggested that the rate of the interconversion between the diastereomeric intermediates **415a** and **415b** (via an $\eta^3-\eta^1-\eta^3$ mechanism) is much faster than the intramolecular nucleophilic attack of the nitrogen nucleophile. In this case, the bulkier alkyl substituent (R^2 = cyclohexyl or *tert*-butyl) of the unsymmetrical carbodiimide may influence the steric interaction during the enantiodeterminating step, resulting in one of the intermediates reacting significantly faster than the other, thus accounting for the high ee's. In the experiments using (*S*)-tol-BINAP as an added chiral phosphine ligand, the intermediate **415b** reacts at a greater rate and thus affords solely the (*R*)-**412** enantiomer.

Scheme 10. Postulated Pathway for Asymmetric Cycloaddition of Vinyloxirane 405a with Unsymmetrical Carbodiimides (Eq 128)



As a further extension of this work, Alper and co-workers have reported the first palladium-catalyzed cycloadditions of 2-vinylthiirane with heterocumulenes and its enantioselective version to form sulfur-containing five-membered-ring heterocycles (eqs 129 and 130).[165]



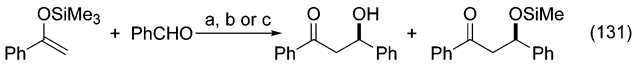


The cyclization of vinylthiiranes **416** with diaryldiimides **406** in the presence of Pd(dba)$_2$−(*R*)-BINAP catalyst afforded thiazolidines **417** in good yields and up to 68% ee (eq 129). However, when the reaction was carried out with keteneimines **418a**,**b**, the thiazolidine products **419a**,**b** were obtained in moderate yields (51−55%) but with a higher ee of 78% in the investigated cases (eq 130).

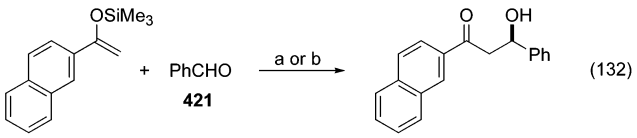
8. Addition of Carbon Nucleophiles to C=O, C=N, and Activated C=C Bonds

8.1. Nucleophilic Addition to C=O Bonds

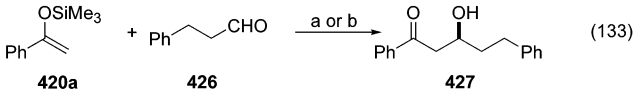
The catalytic aldol reaction that employs a transition metal enolate attracted attention early;[166] however, there had been only a few reports on the catalytic asymmetric aldol reaction proceeding via a chiral transition metal enolate with high enantioselection.[167] Shibasaki and co-workers[168] were the first to describe a synthetically useful asymmetric aldol reaction employing a Pd^{II}−(*R*)-BINAP-derived complex as a catalyst in the presence of AgOTf. Thus, the reaction of silyl enol ether **420a** from acetophenone with benzaldehyde under these conditions gave the aldol adduct **423** in 87% yield and 71% ee (eq 131).



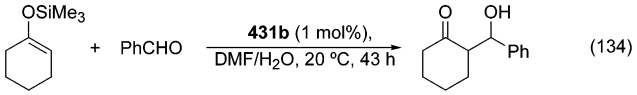
a) $PdCl_2$ (5 mol%), (*R*)-BINAP, AgOTf, MS 4 Å, H_2O-DMF, 23 °C, 13 h, **423**, 87%, 71% *ee*, **422**, 9%, 73% *ee*
b) **431b** (5 mol%), DMF (dry), rt, 1.5 h, **423**, 83%, 72% *ee*, **422**, 15%, 73% *ee*
c) i) **431a** (5 mol%), tetramethyl urea, 0 °C, 24 h, ii) HCl, **422**, 92%, 89% *ee*

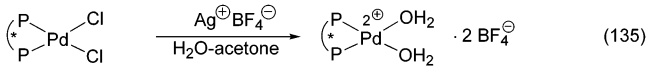


a) **431b** (1 mol%), DMF/H_2O, 22 °C, 18 h, **399**, 82%, 72% *ee*
b) i) **431a** (5 mol%), TMU, 0 °C, ii) HCl, **399**, 89%, 87% *ee*



a) **431b** (2.5 mol%), DMF/H_2O, 23 °C, 44 h, **427**, 78%, 74% *ee*
b) i) **431a** (5 mol%), TMU, 0 °C, ii) HCl, **427**, 88%, 81% *ee*



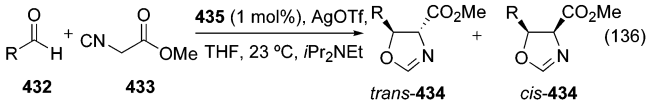


An interesting feature of this reaction was the requirement for water and molecular sieves in the preparation of the active catalyst. In a subsequent paper,[169] the same workers have reported the preparation of the air- and moisture-stable crystalline diaqua-Pd^{II} complexes **431a** and **431b** (eq 135) by reacting the corresponding $PdCl_2$[(*R*)-BINAP] or $PdCl_2$-[(*R*)-tol-BINAP] complexes **430a**,**b** with silver tetrafluoroborate in wet acetone and confirmation of their structures by X-ray crystallography. These catalysts **431a**,**b** are found to be more efficient in enantioselective aldol reactions, yielding various aldol adducts in high yields and ee's (eqs 131−134). A remarkable increase in ee's was observed using (*R*)-BINAP catalyst **431a** in tetramethylurea (TMU) at 0 °C, when the aldol adduct **422** from **420** and benzaldehyde could be obtained in 92% yield and 89% ee (eq 131). Improved yields of the aldol adducts **425** (87% ee) and **427** (81% ee) from the corresponding 2-acetylnaphthalene silylenol ethers **424** and **420** were also obtained under these conditions (eqs 132 and 133).

Recyclable diaqua complexes of type **431**, tailored to a polymeric support, have also been employed recently in enantioselective aldol and Mannich reac-

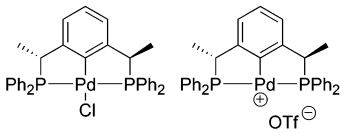
tions.[170] The chemical yield of aldol reaction is strongly improved by addition of water to the solvent.

Zhang and co-workers[171a] have reported an asymmetric aldol reaction between methyl isocyanoacetate and various aldehydes to afford a mixture of cis and trans oxazolines **434** in varying yields and ee's using [(1*R*,1*R*)-2,6-bis[1-(diphenylphosphino)ethylphenyl]-chloropalladium(II) **435** in the presence of AgOTf, generating the active catalytic species **436** (eq 136). Higher enantioselectivities (70−74%) were obtained



432 **433** *trans*-**434** *cis*-**434**

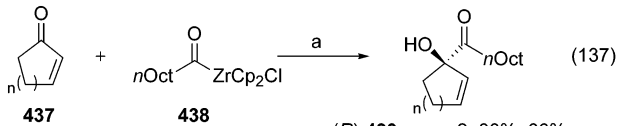
434	R	time [h]	yield [%]	*trans* ee [%]	*cis* ee [%]	*trans* / *cis*
434a	2,4,6-$Me_3C_6H_2$	72	84	26	71	86 / 14
434b	Cy	24	97	11	74	72 / 28
434c	Et	48	91	30	70	91 / 9



435 **436**

for the cis oxazolines **434a**−**c**, whereas the major trans isomers of **434** were found to have much lower ee's.

An unprecedented Pd-catalyzed asymmetric nucleophilic acylation with an "unmasked acyl anion" has recently been reported by Taguchi and co-workers (eq 137).[172] The overall process involves a nucleophilic 1,2-addition of the acylzirconium chloride intermediate to cyclic α,β-unsaturated ketones in the presence of a Pd^{II}−(*R*)-MOP catalyst to afford the ketocarbinol adduct **439a**,**b** in 66−67% ee, although the chemical yield of the adduct **439b** from cyclopentenone was lower (36%) (eq 137). However,



437 n = 2, n = 1 **438**

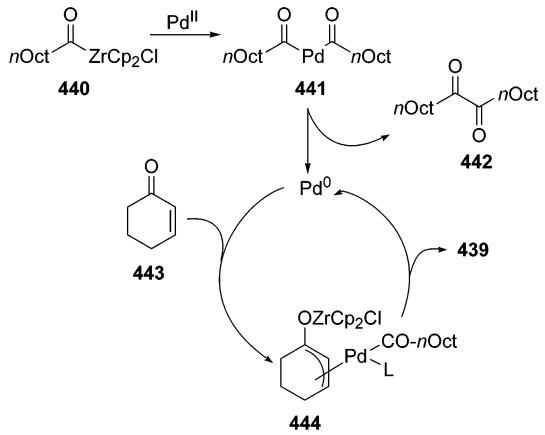
(*R*)-**439a**: n = 2, 88%, 66% *ee*
439b: n = 1, 36%, 67% *ee*

a) $Pd(OAc)_2$ (5 mol%), (*R*)-MOP (10 mol%), toluene, rt, 20 min

the present enantioselective reaction was found to be less efficient for the acyclic α,β-unsaturated ketones (17% ee, 91% yield for benzylideneacetone). A probable mechanism involving the transmetalation of acylzirconium chloride with Pd^{II}, followed by the reductive elimination of Pd^0 from the bisacylpalladium complex, to give the diketone **442** (formed as the side product) has been suggested (Scheme 11).

Subsequent electron transfer from Pd^0 species to cyclohexenone gives the acylpalladium−π-allyl complex **444**, which on reductive elimination of Pd^0 yields the 1,2-acylated product **439**. On the basis of the hypothetical acylpalladium complex **444** and the X-ray structure of an (*R*)-MOP-ligated π-allylpalla-

Scheme 11. Generation of Pd^0 and a Catalytic Cycle for the Acylation of Cyclohexenone with Acylzirconium Chloride



440 **441** **442** **443** **439** **444**

dium complex, it is postulated that the intermediate **444a** is responsible for the chiral induction in the present reaction (Figure 2).

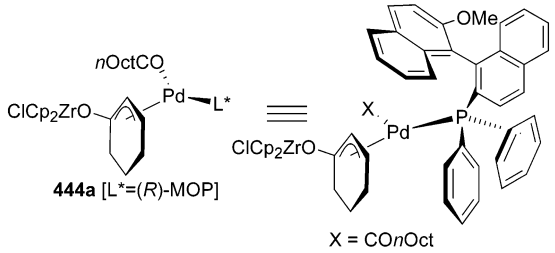


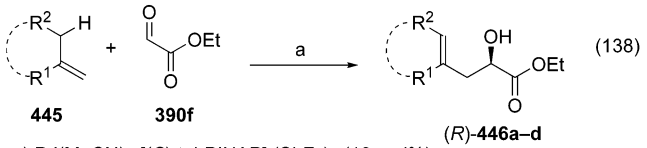
Figure 2. (*R*)-MOP-ligated acylpalladium π-allylic complex **444a**.

Therefore, the sense of the chiral induction under the present reaction conditions indicates the reductive elimination of palladium metal in the (*R*)-MOP-ligated acylpalladium−π-allylic complex **444a** (L* = (*R*)-MOP).

A recent report by Mikami and co-workers[173] describes a highly efficient enantioselective glyoxalate ene reaction catalyzed by chiral BINAP ligands coordinated with Pd^{II} diantimonate catalyst, which provides a simple synthesis of chiral α-hydroxy esters **446** in excellent chemical yields with high enantioselectivity (eq 138). The chiral $Pd(MeCN)_2$−(*S*)-tol-BINAP$(SbF_6)_2$ catalyst, prepared by treatment of Pd(tol-BINAP)Cl_2 with $AgSbF_6$ in acetonitrile, was found to be the most efficient catalyst for this reaction. After optimization of the solvent system and the temperature, the ene reaction of methylenecyclohexane **445a** with ethyl glyoxylate gave the α-hydroxyester **446a** in 97% yield with 88% ee. This catalyst system was found to be equally effective with other 1,1-disubstituted olefins such as α-methylstyrene **445b**, 2-ethyl-1-butene **445c**, and ethylenecyclohexane **445d**, yielding the ene adducts **446b**−**d** in 92−94% yield with high ee's ranging between 73 and 81% for the major diastereomers (eq 138).

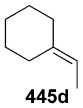
8.2. Nucleophilic Addition to C═N Bonds

The first example of a Pd^{II}-catalyzed asymmetric addition of silylenol ethers to imines[174] was recently reported by Sodeoka and co-workers (eq 139)[175] using

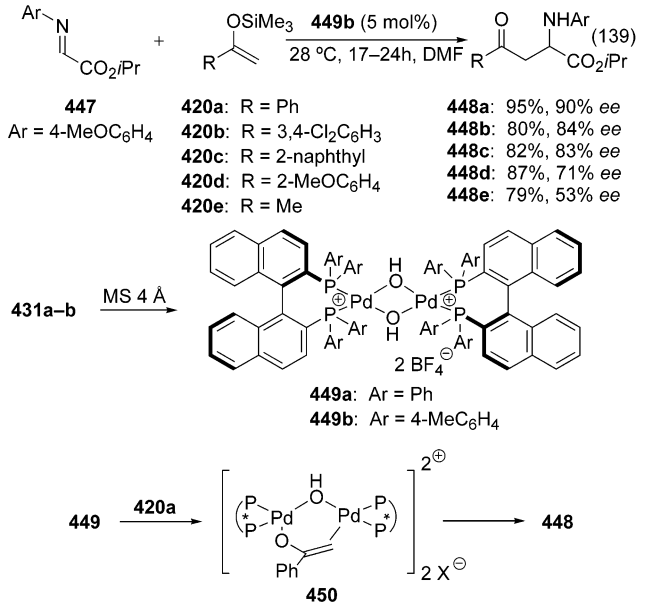


(138)

a) $Pd(MeCN)_2$-[(*S*)-tol-BINAP] $(SbF_6)_2$ (10 mol%), $ClCH_2CH_2Cl$ / toluene (1:2), 60 °C, 4 h

445	yield 446 [%]	*ee* 446 [%]	diastereomeric ratio
 **445a**	97	88	–
 **445b**	93	74	–
 **445c**	92	73 (major)	5.6 / 1
 **445d**	94	81 (major)	2.2 / 1

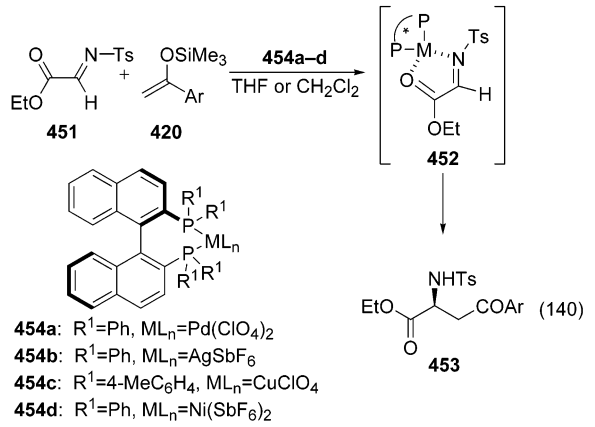
the novel Pd^{II} binuclear complexes **449a**,**b**, prepared by treatment of the earlier described diaqua complexes **431a**,**b** with 4 Å molecular sieves.



(139)

Earlier attempts using diaqua complexes **431** (effective for asymmetric aldol reactions) in this asymmetric Mannich reaction failed to give any enantioselectivity. However, **449b** was found to be quite effective for the condensation of imines such as **447** with silylenol ether **420a**; the desired γ-oxo-α-amino acid derivative **448a** could be obtained in 95% yield and 90% ee (eq 139). The high asymmetric induction observed with **449** in comparison to the diaqua complexes **431** in this reaction has been rationalized as being due to the suppression of the undesirable production of HBF_4. The reaction of other silylenol ethers **420b**−**e** was also shown to give the corresponding optically active acylalanine derivatives **448b**−**e** with good asymmetric induction. With the acetone silylenol ether **420e**, however, the enantioselectivity decreased to 53%. The product acylalanines are potential inhibitors of kynurenine-3-hydroxylase and kynureninase as potential drugs for neurodegenerative disorders, besides being important synthetic intermediates for a wide variety of non-natural amino acids. A detailed mechanistic study of this reaction employing NMR and ESI-MS spectroscopy has been performed by Sodeoka and co-workers.[176] They established the formation of a unique binuclear palladium-sandwiched enolate intermediate **450** using the chiral μ-hydroxy−Pd^{II} complexes **431** and **449** with various counteranions (BF_4^-, TfO^-). This is the first example of a chiral binuclear *O*- and π-bond palladium enolate complex possessing high nucleophilic reactivity.

In another study, Lectka and co-workers[177] have employed water-free late transition metal complexes **454a**−**d** derived from Pd^{II}, Ag^{I}, Cu^{I}, and Ni^{II}, respectively, as chiral Lewis acids for the asymmetric addition of silylenol ethers **420a** to a glyoxylate-*N*-tosylimine (eq 140).



(140)

catalyst [mol%]	temp [°C]	yield 453 [%]	*ee* 453 [%]	Ar	yield 453[a] [%]	*ee* 453
454a (10)	–80	91	80	Ph	63	90
454b (10)	–80	95	90	Ph	66	99
454c (5)	0	91	98	Ph	80	>99
454d (10)	0	92	96	Ph	60	>99

[a] yields and *ee*s after recrystallization

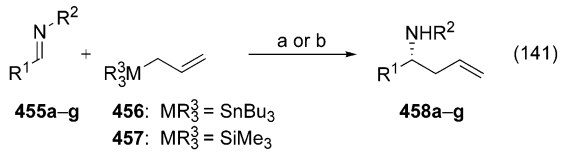
The best results (98% ee) were obtained for **420a** (Ar = Ph) with Cu^{I} catalyst **454c**, whereas the corresponding Pd^{II} complex **454a** afforded the adduct **453** with comparatively lower ee (80%). Although mechanistic studies were performed only on Cu^{I} complex **454c**, these workers have established a Lewis acid-type complexation of **454** with the imine in a bidentate manner to form the chelated complex **452**, unlike Sodeoka's mechanism involving a chiral Pd^{II} enolate intermediate **450**.

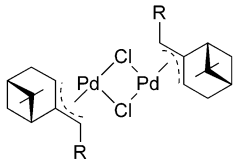
The Pd-catalyzed asymmetric allylation of imines using either allyltributylstannane **456**[178] or allyltrimethylsilane **457**[135] has recently been described by Yamamoto and co-workers using a chiral β-pinene catalyst **459b**, yielding the homoallylamines **458** in good yields and ee's (eq 141). Thus, the allylation of

Table 15. Enantioselective Allylation of Imines 455 Catalyzed by Chiral π-Allylpalladium Complex 459b (Eq 141)

					458 (with **456**)		**458** (with **457**)	
entry	substrate	R^1	R^2	time[a] (h)	yield (%)	ee[b] (%)	yield (%)	ee (%)
1	**455a**	Ph	Bn	90 (46)	62	81	79	80
2	**455b**	Ph	4-$MeOC_6H_5CH_2$	116 (53)	61	82	79	79
3	**455c**	Ph	Ph	20 (36)	74	0	95	3
4	**455d**	Ph	*n*Pr	156 (155)	30	70	34	76
5	**455e**	4-$MeOC_6H_4$	Bn	173 (136)	48	78	60	84
6	**455f**	2-naphthyl	Bn	62 (47)	69	79	88	68
7	**455g**	$PhCH{=}CH_2$	Bn	90 (41)	68	61	77	64

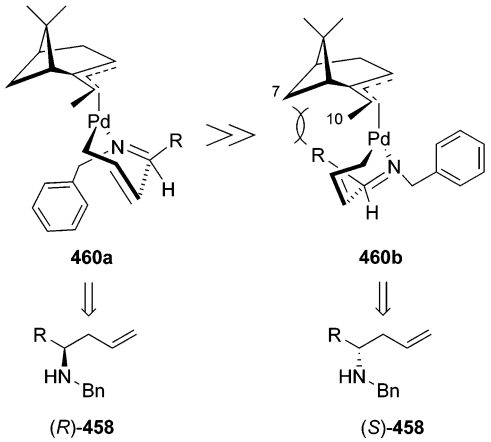
[a] Time in parentheses for the reaction of allylsilane **457**. [b] Yields in DMF solvent.





the imine **455a** with allyltributylstannane **456** in the presence of β-pinene-derived π-allylpalladium catalyst **459b** gave the homoallylamine **458a** in 62% yield and 81% ee under optimized conditions (Table 15, entry 1). On the other hand, allylation of imine **455c** from aniline resulted in 0% ee (entry 3), while the corresponding imine from benzaldehyde and propylamine gave **458d** in 70% ee (entry 4). It has been suggested that the sterically bulkier phenyl group prevents the efficient coordination of the nitrogen atom of the imine to the palladium atom, while a sterically less bulky group should be attached to the nitrogen atom in order to obtain a high ee for the products. In a subsequent paper,[179] the same group reported the smooth asymmetric allylation of these imines **455a**−**g** with the allylsilane **457** in the presence of the chiral Pd−**459b**−TBAF cocatalyst system, thus switching the toxic allylstannanes to allylsilanes (eq 141, Table 15). Comparable yields and ee's of the product homoallylic amines **458a**−**g** were also obtained using allylsilane **457** under these conditions. A probable transition-state model **460** (Scheme 12) has been suggested in which the front side of the η^3-10-methylpinene group of the Pd catalyst is highly crowded by the C-10 methyl group, thus forcing the imine to approach from the less hinderd back side.[179] Subsequent coordination of the imine nitrogen and C−C bond formation takes place through a six-membered cyclic transition state. The reaction thus proceeds through a transition-state model **460a** to give (*R*)-**458** because of the severe steric repulsion between the R group of the imine and the C-7 methylene group in the TS model **460b** (Scheme 12).

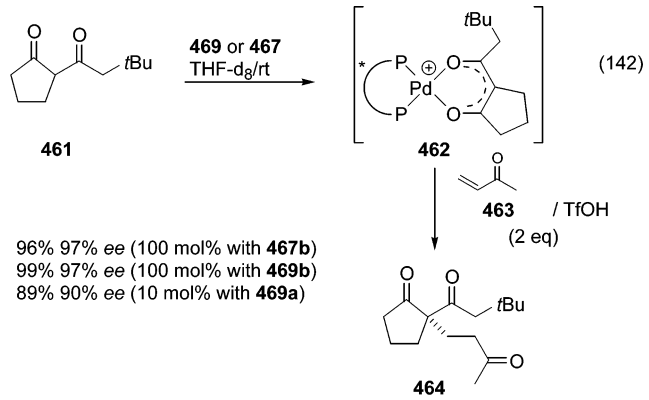
Scheme 12. Probable Transition-State Models for the Pd-Catalyzed Asymmetric Allylation of Imines (Eq 141)

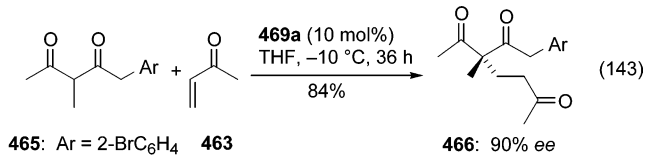


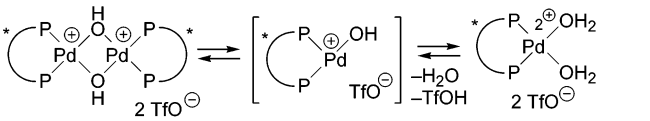
8.3. Michael Additions

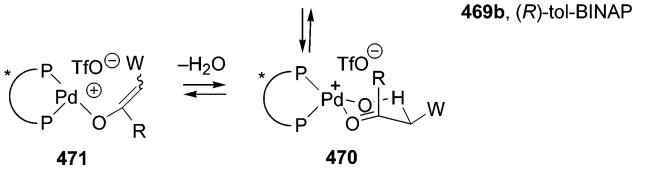
A mechanistically interesting, highly efficient asymmetric Michael addition[180] of 1,3-dicarbonyl compounds with α,β-unsaturated ketones, catalyzed by chiral palladium aqua complexes **467** and **469**, has been reported recently by Sodeoka and co-workers (eqs 142−144).[180] Treatment of 1,3-diketone **461** with either of the diaqua complexes **467** or **469** showed formation of a stable palladium diketonato complex **462**, which did not react with methyl vinyl ketone. However, the addition of 1 equiv of TfOH was found to promote the reaction to afford Michael product **464** in 96−99% yield and with 97% ee (with 100 mol % of catalyst). Under catalytic conditions (10 mol % of **469b**), the reaction of **461** also proceeded smoothy (89%) with high enantioselectivity (90% ee) (eq 142). In addition, the aryl-substituted 1,3-diketone **465** gave the desired triketone **466** in high yield (84%) and with 90% ee, while under ordinary basic conditions (e.g., NEt_3, DBU, KO*t*Bu) the yield was low due to the instability of the product (eq 143). The asymmetric Michael addition is found to be equally successful with a wide range of cyclic and acyclic β-ketoesters **472a**−**e**, yielding the desired Michael adducts **474aa**−**ea** with high enantioselectivities (eq 144, entries 1−5), thus displaying broad generality of the reaction. The corresponding ethyl vinyl ketone **473b** is also shown to be a good acceptor (entry 7).

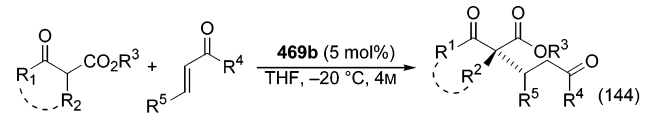
Reducing the catalytic loading to 2 mol % in the case of **472a** did not affect the chemical yield and ee of the product (entry 6). Most unexpectedly, the reaction of β-ketoester **472a** with less reactive β-sub-

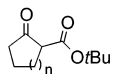
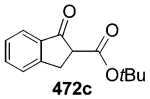
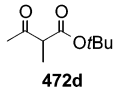
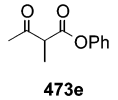










entry	ketoester	enone	time [h]	474	yield [%]	ee [%]
						
1	**472a**: n = 1	**473a**	24	**474aa**	92	92 (*R*)
2[a,b]	**472b**: n = 2	**473a**	72	**474ba**	92	90 (*R*)
3[c,d]	 **472c**	**473a**	48	**474ca**	88	89
4[a,b,c]	 **472d**	**473a**	72	**474da**	88	90
5[b,c]	 **473e**	**473a**	72	**474ea**	69	93 (*R*)
6[e]	**472a**	**473a**	40	**474aa**	93	93
7[a]	**472a**	**473b**	20	**474ab**	84	88
8[a,b]	**472a**	**473c**	36	**474ac**	83 (dr 3.6/1)	97
9[a,b]	**472a**	**473d**	24	**474ad**	89 (dr 8/1)	99

[a] catalyst **469a**, [b] 0 °C, [c] 10 mol% of **469b**, [d] 1M **472c**, [e] 2 mol% of **469a**

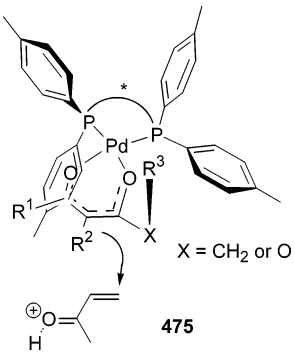


Figure 3. Proposed transition state.

stituted enones **473c** and **473d** afforded the Michael adducts in excellent yield with highest ee of 99% in the case of enone **473d** (entries 8 and 9).

In a unique mechanism in which the Pd complexes **467** and **469** are in equilibrium with the monomeric Pd hydroxo complex **468**, the authors have proposed that **468** acts as both Brønsted base and acid, the former activating the carbonyl compound to give chiral palladium enolate **471** through a favorable six-membered transition state **470** and the latter cooperatively activating the enone. The TfOH selectively activates the enones, and it is interesting that a strong protic acid (TfOH) and inherently basic palladium enolate seem to act cooperatively to promote a carbon−carbon bond-forming reaction.[180]

On the basis of the absolute configuration of the products (*R*) and the requirement of a bulky *tert*-butyl ester in the *β*-ketoesters **472a**−**e** for high enantioselectivity, these workers have proposed transition-state model **475** for this highly enantioselective reaction (Figure 3). The bulky substituent (R^3) would avoid severe interaction with the tolyl group located at one side of the enolate face, thus preferentially blocking the *si* face of the palladium enolate. The incoming enone would thus react with palladium enolate at the *Re* face in a highly enantioselective manner.[180]

9. Cross-Coupling Reactions

Transition-metal-catalyzed cross-coupling between an organometallic species and aryl halides is a powerful synthetic tool and represents one of the most straightforward methods for aryl C−C bond formation.[181]

9.1. Kumada-Type Cross-Couplings

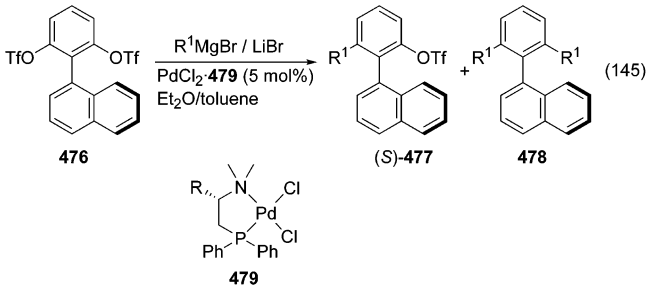
Pioneering work by Hayashi[6,182] has shown that the axially chiral biaryls can be synthesized in high enantioselectivity by a Pd-catalyzed asymmetric Kumada coupling using chiral phosphine ligands (eqs 145 and 146). Thus, a selective substitution of one of the two triflate groups of achiral biaryl triflate **476** by either aryl or alkynyl Grignard reagents in the presence of chiral phosphine ligands **479a**−**c** yielded axially chiral biaryls **477** in high yields and ee's (Table 16, entries 1−4).

In a separate paper,[183] the same workers also reported the Pd-catalyzed selective alkynation of the biaryl triflates **476** with triphenylsilyl-, phenyl-, and alkylethynylmagnesium bromide (Table 16, entries 5−8), with the highest ee of >99% obtained with $PdCl_2$−(*S*)-alaphos as catalyst (entry 6).[183] In all these examples, the enantiomeric purity of the optically

Table 16. Enantioselective Cross-Coupling of Ditriflates 476 with Grignard Reagents Catalyzed by $PdCl_2$·479a−c (Eq 145)

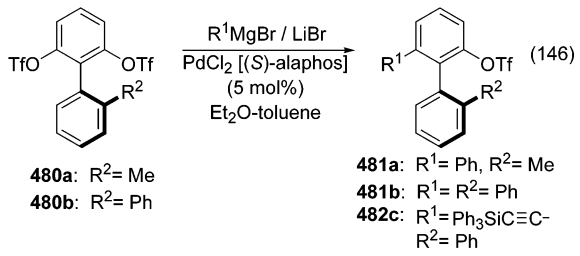
entry	R^1	**479**	time (h)	temp (°C)	yield **477** (%)	yield **478** (%)	ee **477** (%)	ref
1	Ph	**479b**	16	−30	39	0	85 (*S*)	182
2	Ph	**479b**	48	−30	87	13	93 (*S*)	182
3	Ph	**479a**	48	−20	84	10	90 (*S*)	184
4	3-MeC_6H_4[a]	**479a**	72	−20	90	2	95 (*S*)	184
5	$Ph_3SiC{\equiv}C-$	**479a**	6	20	88	10	92 (*S*)	183
6	$Ph_3SiC{\equiv}C-$	**479a**	17	20	53	43	>99 (*S*)	183
7	$Ph-C{\equiv}C-$	**479a**	20	20	84	2	86	183
8	$nPentC{\equiv}C-$	**479c**	70	20	79	15	64	183

[a] LiI additive.



active biaryls **477** has been found to be dependent on the yield of the diarylation (or dialkynylation) product **478**. The enantiomeric purity of the product **477** increases as the amount of diarylation increases (Table 16, entry 1 versus entry 2 and entry 5 versus entry 6), and a kinetic resolution has been demonstrated for the second cross-coupling reaction, resulting in an enhancement of enantiopurity of the monoarylated product. The chiral monoarylated product triflates **477** are shown to be useful chiral building blocks for the synthesis of chiral phosphine ligands by substitution of the triflate group in **477** by either a carboxyl or a diphenylphosphino group by a Pd-catalyzed carbonylation or diphenylphosphinylation, respectively.[184]

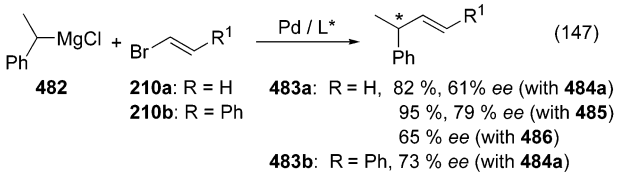
Addition of lithium bromide or iodide was found to be essential for high enantioselectivity as well as for high catalytic activity. The asymmetric phenylation was also successful for the biphenyl triflates **480a** and **480b**, affording the corresponding chiral biphenyls **481** and **482** in high chemical yields and ee's (eq 146).[184]

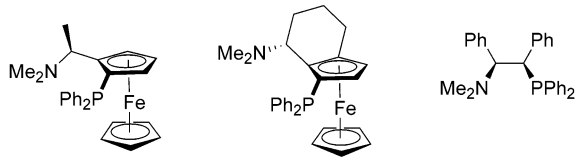


substrate	product	R^1	time [h]	temp [ºC]	yield [%]	*ee* [%]	[Ref.]
480a[a]	**481a**	Ph	72	–10	85	95	[184]
480b[a]	**481b**	Ph	72	–10	80	94	[184]
480b	**481c**	$Ph_3SiC{\equiv}C-$	48	20	88	99	[183]

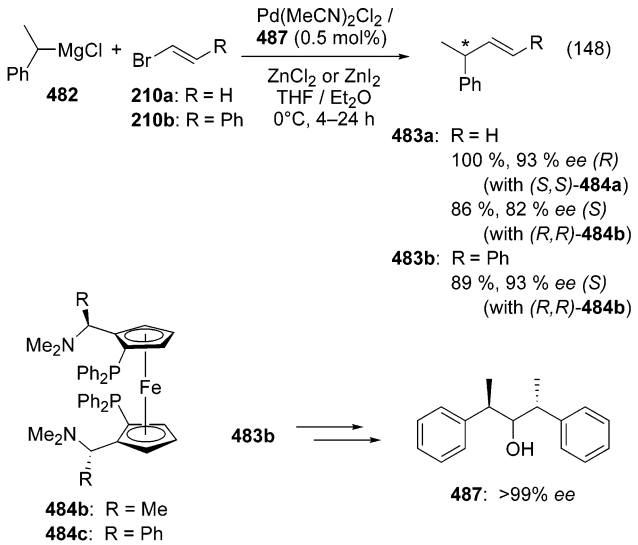
[a] LiI additive

Hayashi and co-workers and others have previously demonstrated high chiral inductions in Pd-catalyzed asymmetric cross-coupling reactions of 1-phenylethylmagnesium chloride or the corresponding zinc reagent with alkenyl bromides using the chiral phosphine ligands **484a**, **485**, and **486** (eqs 147 and



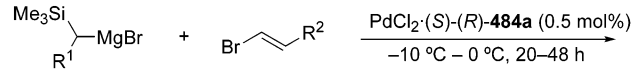


148).[181,185,186] The reaction proceeds more efficiently with zinc reagents[186] than with the corresponding Grignard reagents[187] using a Pd complex catalyst system (eq 148).



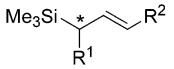
The C_2-symmetric aminoferrocenyl phosphine ligands **484b**,**c**, with aminoalkyl side chains, are shown to be most effective in this reaction, giving the highest ee of 93% for **483a**.[186a] Recently, Knochel and co-workers[187] have reported an efficient cross-coupling of secondary alkylzinc reagents obtained

from phenylethyl Grignard reagents with bromostyrene to provide (*S*)-(*E*)-1,3-diphenyl-1-butene **483b** in high yield (89%) and 93% ee (eq 148). The alkene **483b** could be further converted smoothly into the enantiomerically pure chiral building block **487** in >99% ee.[187] The Pd-catalyzed asymmetric cross-coupling has been successfully applied to the synthesis of optically active silanes (eq 149)[188] by coupling of α-(trimethylsilyl)benzyl and alkylmagnesium bromides with various alkenyl bromides in the presence of Pd complex with the ferrocenyl phosphine ligand (*R*)-(*S*)-PPFA **484a** to give allyl silanes **489** with high ee's.



488a: R^1 = Ph
488b: R^1 = Me

210a: R^2 = H
210b: R^2 = Ph
210c: R^2 = Me
210d: R^2 =

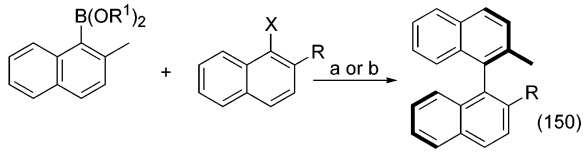


(149)

489a: R^1 = Ph, R^2= H, 42 % 95 % *ee* (*R*)
489b: R^1 = Ph, R^2= Me, 72 % 85 % *ee* (*R*)
489c: R^1 = R^2= Ph, 93 % 95 % *ee* (*R*)
489d: R^1 = Me, R^2= Ph, 88 % 93 % *ee* (*R*) (with Et_3Si)
489e: R^1 = Me, R^2= , 51 %, 45 % *ee* (*S*) (with $PhMe_2Si$)

9.2. Suzuki-Type Cross-Couplings

The first reports of a Suzuki coupling for the synthesis of axially chiral biaryls have been published recently simultaneously by Cammidge[189] and Buchwald[190] (eqs 150−153). Thus, under optimized reac-

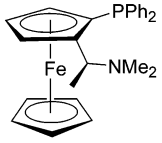


(150)

490a: R^1= H
490b: R^1= -CH_2CH_2-

491a: X = I, R = H
491b: X = I, R = Me

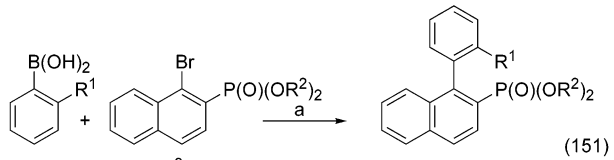
(*R*)-**492a**: R = H
(*R*)-**492b**: R = Me



a) $PdCl_2$ (3 mol%), **484a** (6 mol%), $Ba(OH)_2$, DME-H_2O, 19 h, **492a**, 44%, 63% *ee*
b) $PdCl_2$ (3 mol%), **484a** (6 mol%), CsF, DME, 6 d, **492b**, 50%, 85% *ee*

484a: (*S*)-(*R*)-PPFA

tion conditions, Cammidge and co-workers[189] could obtain the binaphthyl **492b** with a maximum ee of 85% in a moderate yield (50%) by reacting α-naphthyl iodide **491b** with borate ester **490b**, using a chiral Pd catalyst derived from the monophosphine ligand (*S*)-(*R*)-PFNMe (or PPFA) **484a** (eq 150). In contrast, the corresponding 2-unsubstituted binaphthyl **492a** was formed, but in a moderate yield (44%) and a rather low ee (63%), by coupling of **491a** and **490a** under similar reaction conditions. Buchwald and coworkers[190] have published a detailed preliminary report on the first example of a catalytic enantioselective Suzuki cross-coupling for the preparation of functionalized chiral biaryls, employing the binaphthyl-based electron-rich chiral ligand **499** (eqs 151−153).



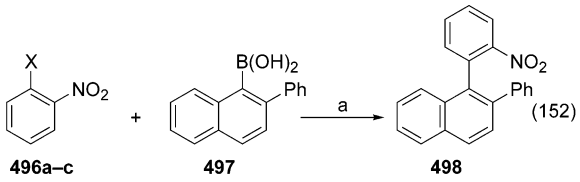
(151)

493a–d
494a: R^2= Et
494b: R^2= Me
495aa–495da
495ab

a) $Pd_2(dba)_3$·(*S*)-(+)-**499**, K_3PO_4, toluene

493	R^1	**494**	Pd [mol%]	temp [°C]	time [h]	**495**	yield [%]	*ee* [%]
493a	Me	**494a**	4	70	88	**495aa**	98	87[a]
493b	Et	**494a**	8	70	88	**495ba**	90	92[a]
493b	Et	**494a**	1	70	24	**495ba**	94	92[b]
493c	*i*Pr	**494a**	10	80	140	**495ca**	83	85[a]
493c	*i*Pr	**494a**	2	80	24	**495ca**	89	85[b]
493d	Ph	**494a**	3	60	48	**495da**	74	74[a]
493a	Me	**494b**	0.2	60	24	**495ab**	95	86[b,c]

[a] with 2 eq of K_3PO_4; [b] with 3 eq of K_3PO_4; [c] 3 eq of NaI

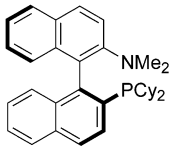


(152)

496a–c **497** **498**

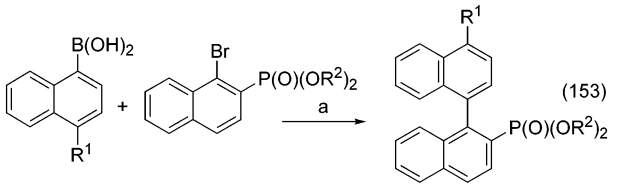
a) $Pd_2(dba)_3$·(*S*)-(+) **453**, K_3PO_4 (2–3 eq), toluene, 70 °C, 48 h

496	X	Pd [mol%]	yield **498** [%]	*ee* **498** [%]
496a	I	3	86	73
496b	Br	10	82	72
496c	Cl	4	83	72



(*S*)-(+)-**499**

Thus, by using (*S*)-(+)-**499** in the Suzuki coupling between various boronic acids **493a**−**d** and the bromides **494a**,**b**, the chiral 1-arylnaphthalenes **495** could be obtained in high overall yields with ee's ranging from 74 to 92% (eq 151). Similarly, the nitro-substituted biaryls **498** could also be synthesized in high yields and ee's by coupling of boronic acid **497** and *o*-halonitrobenzenes **496a**−**c** (eq 152). K_3PO_4 was found to be a better base in these reactions than KF, CsF, or KO*t*Bu. Furthermore, by taking 3 equiv of K_3PO_4, the reactions were found to be faster and could be performed with even 0.2−0.24 mol % of the catalyst without effecting the ee's of the products. Similarly, the axially chiral binaphthyls **501** could also be obtained in high yields and good ee's (57−73%) (eq 153) by a Suzuki cross-coupling of the boronic acids **500a**,**b** and the bromophosphonates **494a**,**b** under similar conditions using (*S*)-(+)-**499** as chiral ligand. The phosphonate moiety present in biaryl **495** is shown to be suitable for their further functionalization so that they could be converted into the new chiral phosphine ligand **502** in 86% yield and 99% ee.



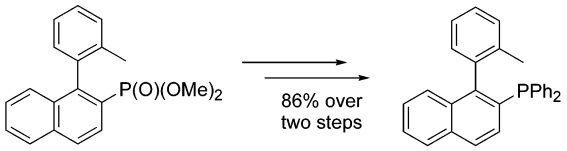
500a: R^1= H **494a**: R^2= Et
500b: R^1= OMe **494b**: R^2= Me

501aa: R^1= H, R^2= Et, (*S*)
501ba: R^1= OMe, R^2= Et
501bb: R^1= OMe, R^2= Me

a) $Pd_2(dba)_3$·(*S*)-(+)-**499**, K_3PO_4 (2 eq), toluene

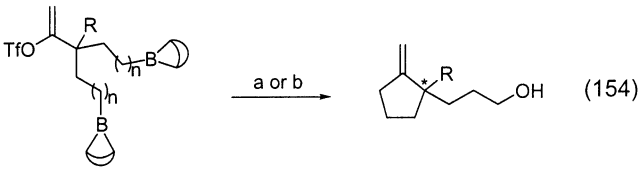
500	494	Pd [mol%]	temp [°C]	time [h]	501	yield [%]	*ee* [%]
500a	**494a**	4	40	40	**501aa**	97	57
500b	**494a**	4	40	92	**501ba**	97	71[a]
500b	**494b**	2	40	48	**501bb**	80	73

[a] with 3 eq K_3PO_4



495ab (–)-**502**: 99% *ee*

The possibility of creating a stereogenic tertiary or quaternary aliphatic center by an asymmetric Suzuki coupling of prochiral alkylboranes has been recently demonstrated by Shibasaki and co-workers (eq 154).[191]



503a: R = H, n = 2
503b: R = CH_2OTBS, n = 2

(R)-**504a**: R = H
(R)-**504b**: R = CH_2OTBS

ent-**233**: *(S)-(R)*-BPPFOAc

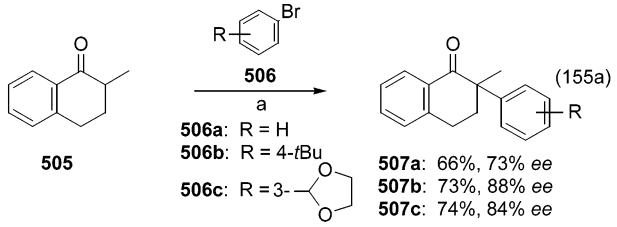
484a: *(S)-(R)*-PPFA

a) (i) $Pd_2(dba)_3$ (10 mol%), *ent*-**233** (20 mol%), K_2CO_3, THF, 40 °C 12 h; (ii) NaOH, H_2O_2, **504a**, 58%, 28% ee
b) (i) $Pd_2(dba)_3$ (10 mol%), **484a** (20 mol%), K2CO3, THF, 40 °C 12 h; (ii) NaOH, H_2O_2, **504b**, 42%, 31% ee

Thus, the prochiral triflates **503a**,**b**, on treatment with the Pd complex of the ligands **484a** or *ent*-**233**, followed by an oxidative workup, afforded the product methylenecyclopentanes **504a**,**b** through intramolecular cross-coupling, although in moderate yields and low ee's (28 and 31%).

10. Arylation of Ketone Enolates

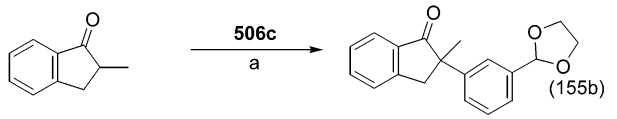
A first example of a highly enantioselective Pd-catalyzed arylation of ketone enolates to furnish ketones with quaternary carbon centers has been recently published by Buchwald and co-workers (eqs 155a–c).[192] The arylation of 2-methyltetralone with the various substituted bromobenzenes **506a**–**c** in



505

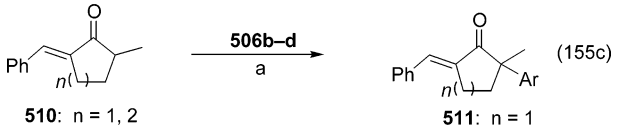
506a: R = H
506b: R = 4-*t*Bu
506c: R = 3-

507a: 66%, 73% *ee*
507b: 73%, 88% *ee*
507c: 74%, 84% *ee*



508

509: 79%, 70% *ee*



510: n = 1, 2

511: n = 1

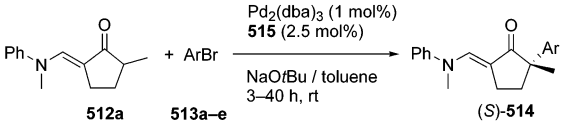
a) $Pd(OAc)_2$ (*S*)-BINAP (10–20 mol%), NaO*t*Bu, toluene, 100 °C

511	Ar	yield [%]	*ee* [%]
511a	4-*t*BuC_6H_4	75	98
511b[a]	3-	81	95
511c	3-MeC_6H_3	80	94

[a] NaHMDS and $Pd_2(dba)_3$

the presence of $Pd(OAc)_2$ and (*S*)-BINAP proceeded with good enantioselectivities in the range of 73–88% and 66–74% chemical yield (eq 155a). Similarly, 2-methylindanone gave the 2-aryl-2-methylindanone **509** in 79% yield with 70% ee under similar reaction conditions (eq 155b). Interestingly, the arylation of the α′-blocked-α-methylcyclopentanone **510** also proceeded with high yields and with excellent ee's (94–98%) (eq 155c). On the other hand, the corresponding 2-methylcyclohexanone yielded product **511** ($n = 2$) with various aryl iodides under these conditions in very low ee's using the same base or NaHMDS.

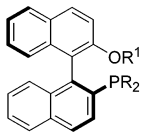
Buchwald and co-workers have recently reported a new catalytic system prepared from $Pd_2(dba)_3$ and bulky dialkylphosphino-binaphthyl ligands (*S*)-**515a**–**c**, displaying higher reactivity than the previous Pd-$(OAc)_2$/(*S*)-BINAP system.[193] The arylation reactions could be effected at room temperature and with only 2 mol % of Pd catalyst (eq 156a).[193] They have also introduced a more efficient blocking group, i.e., an *N*-methyl-anilinomethylene moiety, which could be easily removed after arylation reactions. The corresponding (*S*)-2′-(diisopropylphosphino)-2-(1-naphthylmethoxy)-1,1′-binaphthyl ligand **515a** proved to be the most efficient ligand in asymmetric arylation of 2-methyl-5-*N*-methylanilinomethylene cyclopentanone **512a**, yielding (*S*)-**514** with a quaternary stereogenic center with high ee's (89–94%) (eq 156a). A comparison of the α-arylation of various α-alkyl-substituted cyclopentanones **512a**–**c** with the ligand **515a** and (*S*)-BINAP–Pd complexes showed that, with (*S*)-BINAP ligand, the highest ee was observed when employing cyclopentanone with the largest α-alkyl substituent (eq 156b) (entry 6 vs entry 4 vs entry 2, *n*-pentyl > *n*-propyl > methyl), whereas



(156a)

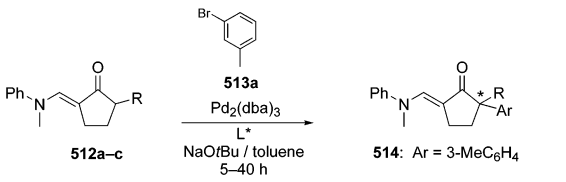
entry	ArBr	L*	yield [%]	*ee* [%]
1	3-MeC_6H_4Br (**513a**)	**515a**	85	94
2	4-MeC_6H_4Br (**513b**)	**515a**	84	93
3	3-$MeOC_6H_4Br$ (**513c**)	**515a**	80	89
4	4-$MeOC_6H_4Br$ (**513d**)	**515a**	80	94
5	4-*t*BuC_6H_4Br (**513e**)	**515a**	84	93
6	4-*t*BuC_6H_4Br (**513e**)	(*S*)-BINAP[a]	70	89
7	4-*t*BuC_6H_4Br (**513e**)	**515b**	88	86
8	4-*t*BuC_6H_4Br (**513e**)	**515c**	79	88

[a] 10 mol% at 100 °C in toluene



(*S*)-**515a**: R = *i*Pr; R^1= CH_2 (1-naphth)
(*S*)-**515b**: R = *i*Pr; R^1= Me
(*S*)-**515c**: R = *i*Pr; R^1= CH_2Bn

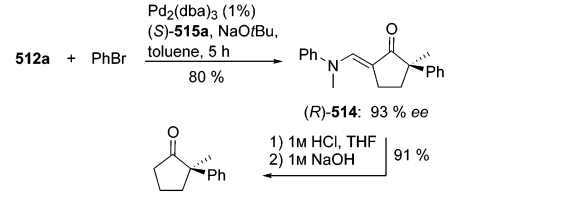
ee's observed with the ligand **515a** were less sensitive to the α-alkyl substituents, and the α-methyl-substituted cyclopentanone **512a** was arylated in the highest ee with this ligand (eq 156b, entry 1). Sub-



(156b)

	512	R	L*	temp [°C]	514	yield [%]	*ee* [%]
1	**512a**	Me	(*S*)-**515a**[a]	RT	**514a**	85	94 (*R*)
2	**512a**	Me	(*S*)-BINAP[b]	100	**514a**	70	80 (*S*)
3	**512b**	*n*Pr	(*S*)-**515a**[a]	RT	**514b**	85	88 (*R*)
4	**512b**	*n*Pr	(*S*)-BINAP[b]	100	**514b**	74	91 (*S*)
5	**512c**	*n*Pent	(*S*)-**515a**[b]	RT	**514c**	86	91 (*R*)
6	**512c**	*n*Pent	(*S*)-BINAP[c]	100	**514c**	75	93 (*S*)

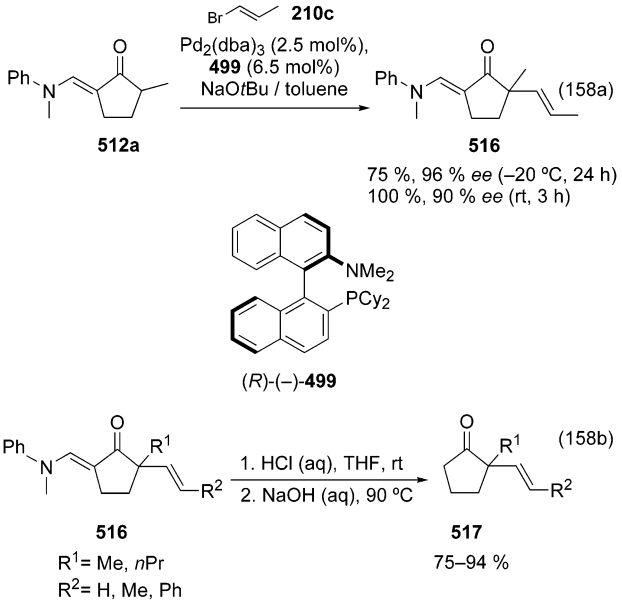
[a] 2 mol% Pd, RT, ligand / $Pd_2(dba)_3$= 2.5 : 1,
[b] 2.5 mol% $Pd_2(dba)_3$, L* / $Pd_2(dba)_3$= 2.5 : 1,
[c] 10 mol% $Pd(OAc)_2$



(157)

sequent removal of the blocking group afforded the α-arylated-α-methylcyclopentanones **199** without loss of enantiopurity (eq 157).[193]

In a continuation of the above studies, Buchwald and co-workers recently have also developed a new protocol for efficient catalytic asymmetric vinylation of 2-alkylcyclopentanone derivatives **512** using a Pd−2-(dimethylamino)-2′-(bicyclohexyl)-naphthyl (**499**) complex in high yields and ee's up to 96% (eq 158)[194] at −20 °C. Extension of the reaction to a series of α-blocked cycloalkanones **512** with various alkenyl bromides using $Pd_2(dba)_3$/**499** catalyst provides a

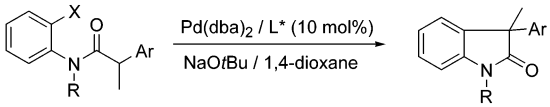


(158a)

(158b)

general method for obtaining a variety of α-vinylcyclopentanones **516** in good yields with moderate to high levels of enantioselectivity (Table 17).[194] Deprotection of the 5-(*N*-methylanilinomethylene) group in these cyclopentanones under mild conditions leads to the first general route to α-vinyl-α-alkylcyclopentanones in highly enantiomerically enriched forms (eq 158b).

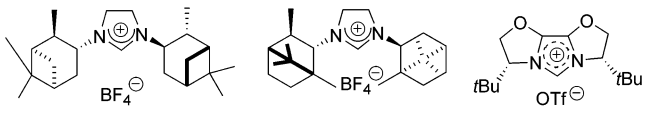
Hartwig and co-workers have recently reported a novel enantioselective synthesis of oxindoles by palladium-catalyzed intramolecular α-arylation of amides (eq 159).[195] Use of the new optically active heterocy-



(159)

entry	substrate	R	X	L*	temp [°C]	time [h]	yield [%]	*ee* [%]
1	**518a**	Bn	Br	**520**	25	24	88	67
2[a]	**518a**	Bn	Br	**521**	25	24	80	71
3	**518a**	Bn	Br	**521**	10	40	75	76
4	**518a**	Me	Br	**521**	0	40	27	70
5	**518a**	Me	Cl	**520**	50	26	91	69
6[b]	**518b**	Me	Br	**521**	25	24	74	57
7	**518b**	Me	Br	**522**	20	14	95	43

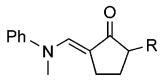
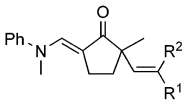
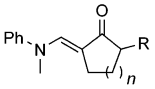
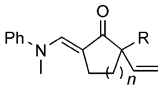
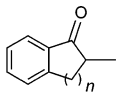
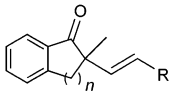
[a] 2 % Pd / L* ; [b] 5 % Pd / L*



520 **521** **522**

clic carbene ligands **520** and **521** gave substantial enantioselectivity (up to 76%) in the formation of α-naphthyl-α-methyloxindole **519a**. In contrast, a variety of optically active phosphine ligands that were tested gave poor enantioselectivity. A higher ee for the α-naphthyl-α-methyloxindole **519a** was observed after lowering the temperature for the Pd

Table 17. Coupling between Ketone, Enolates, and Vinyl Halides Catalyzed by $Pd_2(dba)_3$/(*R*)-(−)-499 (Eq 158a)

entry	Ketone	Vinyl halide	**516**	% yield	% *ee*
					
1	**512a**: R = Me	 **210c**	R^1= Me, R^2= H	95[a]	90
2	**512a**: R = Me	 **210a**	R^1= R^2= H	94[a]	92
3	**512a**: R = Me	 **210b**	R^1= Ph, R^2= H	92[a]	89
4	**512a**: R = Me	 **518**	R^1= R^2= Me	95[b]	71
					
5	**512b**: *n* = 1, R = *n*Pr	**210a**	*n* = 1, R = *n*Pr	86[b]	90
6	**512c**: *n* = 1, R = *n*Pent	**210a**	*n* = 1, R = *n*Pent	84[b]	92
7	**512d**: *n* = 2, R = Me	**210a**	*n* = 2, R = Me	78[b]	50
					
8	**512e**: *n* = 1	 **210c**	*n* = 1, R = Me	95[a]	74
9	**512f**: *n* = 2	**210a**	*n* = 2, R = H	96[a]	80

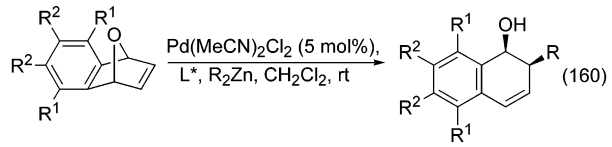
[a] With 1 mol % $Pd_2(dba)_3$. [b] With 2.5 mol % $Pd_2(dba)_3$. Pd:L ratio 1:1.25.

complex with the ligand **521** (entry 3 vs entry 2). With both ligands, reaction of bromo-substituted **518a** (R = Me) occurred with enantioselectivity similar to that of reaction with the chloro-substituted derivative (entries 4 and 5). With α-phenylamide **518b** (R = Me), the oxindole **519b** (R = Me) was obtained in good yield but with moderate ee of maximum 57% (entry 6) with ligand **521**. In a recent study, Glorius and co-workers have examined Pd-catalyzed enantioselective intramolecular α-arylation of α-phenylamide **518b** (Ar = Ph, R = Me) using chiral imidazolium triflate **522**, affording oxindole **519b** (R = Me) in excellent yield but with low ee (43%) (eq 159, entry 7).[196]

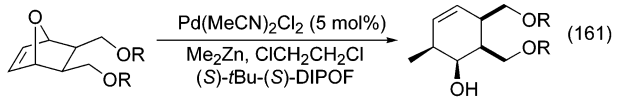
11. Other C–C Bond-Forming Reactions

11.1. Alkylative Ring Opening of Oxabicycles

The carbanionic alkylative ring opening of oxabicyclo[2.2.1]- or -[3.2.1]benzonorbornene systems to give substituted tetrahydronaphthalenes is a well-established reaction which has been extensively studied by Lautens and co-workers.[197] The same group has reported the enantioselective version of this reaction in two recent publications.[198] In the Pd-catalyzed enantioselective carbanionic ring opening of several oxabenzonorbornenes **523** with either dimethyl- or diethylzinc, the best results were obtained with Pd catalysts containing the chiral (*R*)-tol-BINAP or *i*Pr-POX ligand **121a** (eq 160) (Table 18). Interestingly, it was found that (*R*)-tol-BINAP-provided the highest ee's for the addition of di-

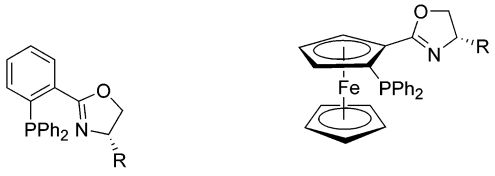


523 **524**



525a: R = PMB
525b: R = TBDPS
525c: R = Me

526a: 87%, 91% *ee*
526b: 90%, 98% *ee*
526c: 58%, 91% *ee*



121a: R= *i*Pr, (*S*)-*i*Pr-POX
121b: R= *t*Bu, (*S*)-*t*Bu-POX

124a: R= *i*Pr, (*S*)-*i*Pr-DIPOF
124b: R= *t*Bu, (*S*)-*t*Bu-DIPOF

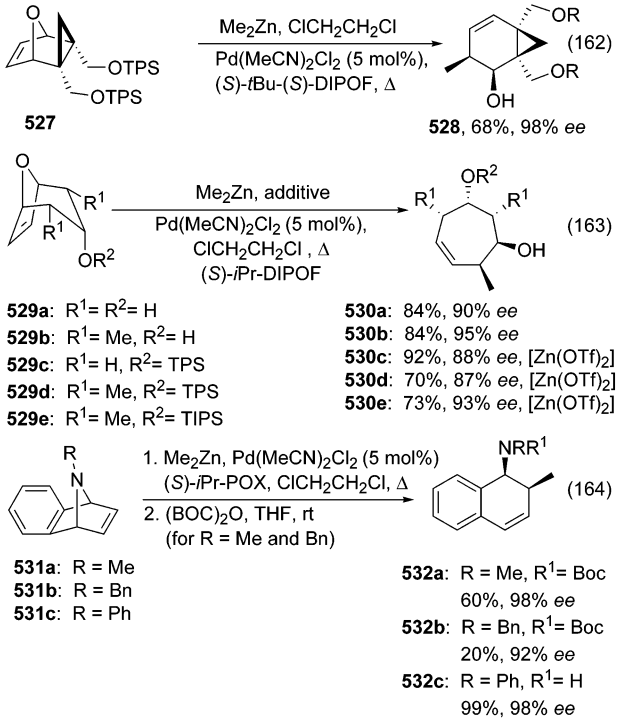
Table 18. Enantioselective Additions to Oxabenzonorbornadienes (Eq 160)

entry	R	R^1	R^2	yield **524** (%)	ee **524** (%)	L*
1	Me	H	H	90 (80)[a]	89 (97)[a]	(*S*)-*i*Pr-POX
2	Me	H	F	87 (93)[a]	90 (96)[a]	(*S*)-*i*Pr-POX
3	Me	H	$-OCH_2O-$	85 (94)[a]	91 (97)[a]	(*S*)-*i*Pr-POX
4	Et	H	H	98	96	(*R*)-tol-BINAP
5	Et	H	F	89	92	(*R*)-tol-BINAP
6	Et	H	$-OCH_2O-$	91	92	(*R*)-tol-BINAP
7	$TMSCH_2$	H	H	81	92	(*R*)-tol-BINAP

[a] Yields and ee's in parentheses were obtained with *t*Bu-POX **125b** (ref 199b).

ethylzinc (entries 4−6), whereas *i*Pr-POX **121a** worked best when dimethylzinc was used as alkylating agent (entries 1−3).[198a] However, so far no satisfactory explanation for the observed difference in enantioselectivities with diethyl- and dimethylzinc in the presence of the two chiral ligands could be given.

The alkylative enantioselective ring opening could also be achieved with less reactive substrates such as **525**, **527**, and **529** (eqs 161−163).[198b] The best ee's



527

528, 68%, 98% *ee*

529a: R^1= R^2= H
529b: R^1= Me, R^2= H
529c: R^1= H, R^2= TPS
529d: R^1= Me, R^2= TPS
529e: R^1= Me, R^2= TIPS

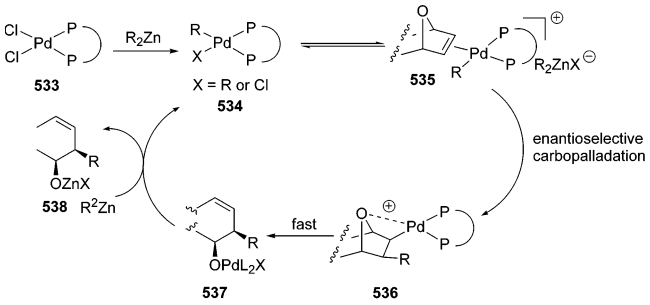
530a: 84%, 90% *ee*
530b: 84%, 95% *ee*
530c: 92%, 88% *ee*, $[Zn(OTf)_2]$
530d: 70%, 87% *ee*, $[Zn(OTf)_2]$
530e: 73%, 93% *ee*, $[Zn(OTf)_2]$

531a: R = Me
531b: R = Bn
531c: R = Ph

532a: R = Me, R^1= Boc
60%, 98% *ee*
532b: R = Bn, R^1= Boc
20%, 92% *ee*
532c: R = Ph, R^1= H
99%, 98% *ee*

for the ring opening of **525a**−**c** were obtained using ferrocene-derived *t*Bu-(*S*)-DIPOF ligand **124b**. In the case of **525b**, the cyclohexenol **526b** was formed in 90% yield and with 98% ee. The other [2.2.1] substrate, **527**, containing a cyclopropane ring, gave a slightly lower yield (68%) but a comparable ee (98%) (eq 162). Similarly, the extension of these studies to [3.2.1] bicyclic substrates **529a**−**e** yielded the cycloheptene diols **530a**−**e** in high yields and ee's (eq 163). The addition of $Zn(OTf)_2$ (**530c**−**e**) in this reaction improved in a few cases the chemical yields of the products without affecting the ee's. Good results were also obtained for asymmetric ring-opening studies of azabicyclic systems **531a**−**c** (eq 164), which are shown to be less reactive than their oxygen counterparts. Using the POX ligand **121a**, excellent ee's for

Scheme 13. Proposed Mechanism for the Pd-Catalyzed Enantioselective Ring Opening of Oxabicyclic Alkenes with Dialkylzinc



533 **534** **535** **536** **537** **538**

the products **532a**−**c** could be obtained, although the R group on the nitrogen has been found to affect the chemical yields (not the ee's) with the phenyl group (**432c**) giving the best yields (eq 164).[198b]

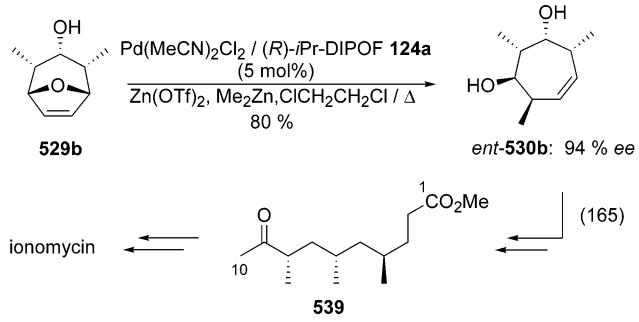
In a detailed mechanistic study[199] involving trapping of a carbometalated product and a successful reaction with an alkylpalladium species, Lautens and co-workers provided strong evidence in favor of an enantioselective carbopalladation as the key step in the mechanism and ruled out formation of π-allylpalladium species by initial cleavage of the C−O bond. The proposed mechanism (Scheme 13) involves the generation of a palladium alkyl species by transmetalation with the dialkylzinc, which then binds the alkene substrate with loss of X^- assisted by Lewis acid zinc reagent to give the cationic palladium species **535**; an enantioselective carbopalladation then takes place to give the intermediate **536**.

Subsequent β-oxygen elimination (**537**) followed by transmetalation with dialkylzinc regenerates the catalyst and gives the zinc alkoxide product **538**. The dialkylzinc functions in both, the transmetalation to palladium and the forming of the reactive cationic palladium species, in the latter step as a Lewis acid.

Recently, Lautens and co-workers[200] have applied palladium-catalyzed enantioselective alkylative ring opening in conjunction with nickel-catalyzed reductive ring-opening methodology for the synthesis of the C_1−C_{10} fragment **539** in total synthesis of polyether antibiotic ionomycin (eq 165).[200]

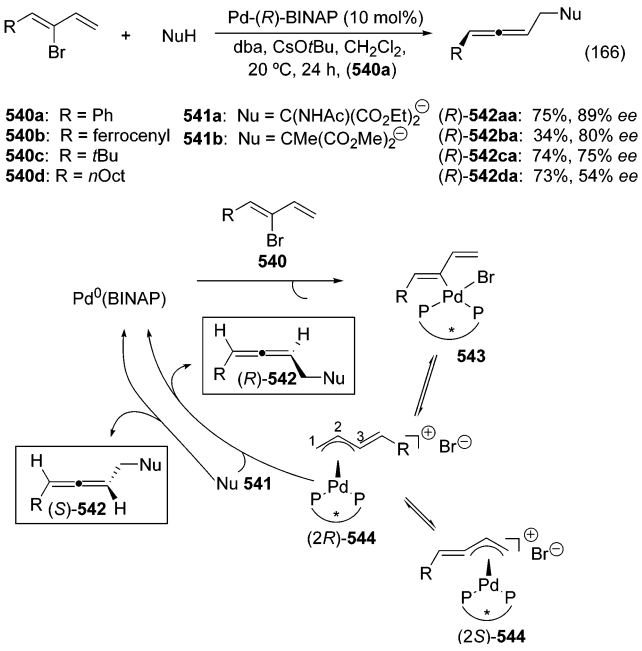
11.2. Synthesis of Axially Chiral Allenes

In a recent paper, Hayashi and co-workers[201a] have reported the first example of a transition metal Pd-catalyzed enantioselective synthesis of allenes (eq 166). Thus, the reaction of the bromo-1,2-diene **540a** with carbon nucleophiles such as **541a** in the presence of Pd−(*R*)-BINAP afforded the axially chiral



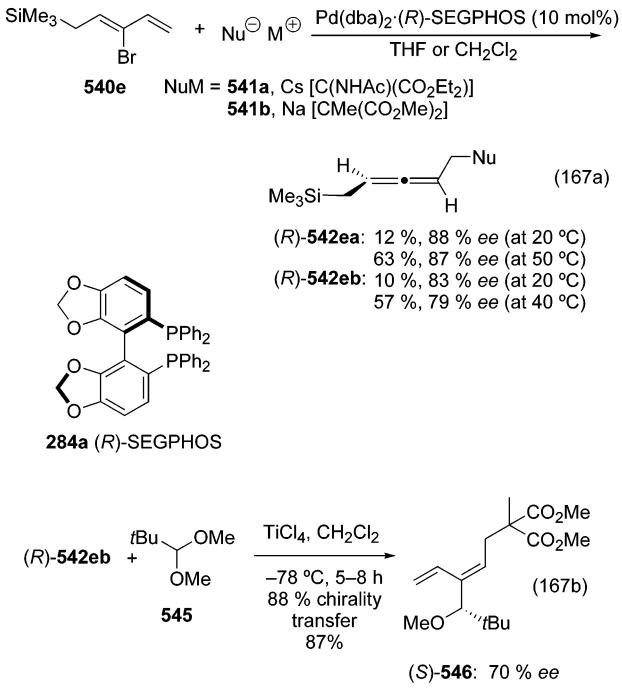
allenes **542aa** as product in 75% yield and 89% ee. The choice of the carbon nucleophile and the countercations (CsO*t*Bu) is shown to be important for a high enantioselectivity, since the analogous reaction with bases such as NaH or KO*t*Bu showed a lower enantioselectivity (52−72%). The other substituted bromobutadienes **540b**−**d** also yielded the optically active allenes **542ba**−**542da** with good to moderate enantioselectivies after reaction with **541a** under identical conditions (eq 166). A probable mechanism for the formation of asymmetric allenes from **540** is shown in Scheme 14.

Scheme 14. Catalytic Cycle of the Enantioselective Synthesis of Allenes (Eq 166)



The proposed key intermediate, i.e., the *exo*-alkylidene−π-allylpalladium species **544**, exists as an equilibrium mixture of two diastereomeric Pd intermediates, (2*R*)-**544** and (2*S*)-**544**, to yield either (*S*)- or (*R*)-allenes **542** by reaction with the carbon nucleophile **541**. The controlling factors for enantioselectivity of the allene formation appear to be (a) the relative reactivity of the diastereomeric (2*R*)-**544** and (2*S*)-**544** respectively toward **541** and (b) the equilibrium between these two intermediates. During the course of these studies, it was observed that the dibenzalacetone (DBA) released from the catalyst precursor has an effect on the observed high enantioselectivity of the formed allenes. In the absence of $Pd(dba)_2$ complex (or added DBA), the allenes **542** were formed in very low ee's. These workers have isolated the intermediate benzylidene π-allylpalladium species as BAr_4^{F-} ($Ar^F = C_6H_5$-3,5-$(CF_3)_2$) salt and reacted it with the carbon nucleophile **541b**. On the basis of these experiments, they have suggested that the coexisting DBA accelerates the equilibrium between the two diastereomers of π-allylpalladium species. Although the mechanism of this DBA-induced acceleration process is not yet clear, experimental studies have clearly demonstrated that the coexistent DBA accelerates the epimerization of **544** by a factor of 12−25, which is probably a main factor for the unique positive influence of DBA on the enantioselectivity in the present reaction.

In a recent study, Hayashi and co-workers have extended this reaction for the synthesis of axially chiral (allenylmethyl)silanes (eq 167a).[201b] Using (*R*)-

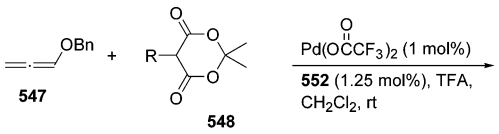


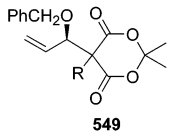
BINAP, the allenes **542ea**,**b** were obtained in low yields and ee's, whereas the use of (*R*)-SEGPHOS (**284a**) as ligand gave allenes **542ea**,**b** in up to 88% enantioselectivity. The rection of allenylsilanes with acetals in the presence of $TiCl_4$ gave 1,3-diene derivatives **546** (via an $S_{E'}$ pathway) with high stereoselectivity and up to 88% chirality transfer from the axially chiral allenes (eq 167b).

11.3. Hydrocarbonation of Allenes

A highly efficient palladium-catalyzed asymmetric addition of pronucleophiles such as Meldrum's acid and azalactone to benzyloxyallene via an initial hydropalladation process has been recently reported by Trost and co-workers (eqs 168 and 169).[202] The key for good reactivity and selectivity in this reaction is found to be the specific control of pH to facilitate the hydropalladation process to give the π-allylpalladium complex (Scheme 15).

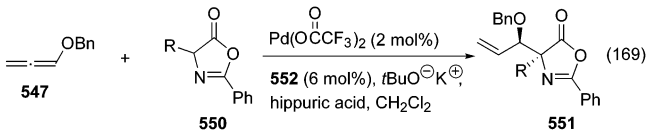
Thus, in the reaction of the Meldrum's acid derivatives **548** with benzyloxyallene, the best ee's (>90%) were obtained using palladium trifluoroacetate in the





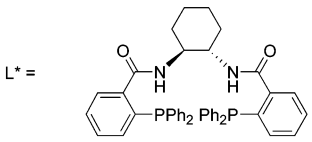
(168)

entry	R	yield [%]	*ee* [%]
1	Me	75	99
2	$H_2C=CHCH_2$	82	96
3	$PhCH_2$	90	91
4	$2\text{-}C_4H_3OCH_2$	81	94



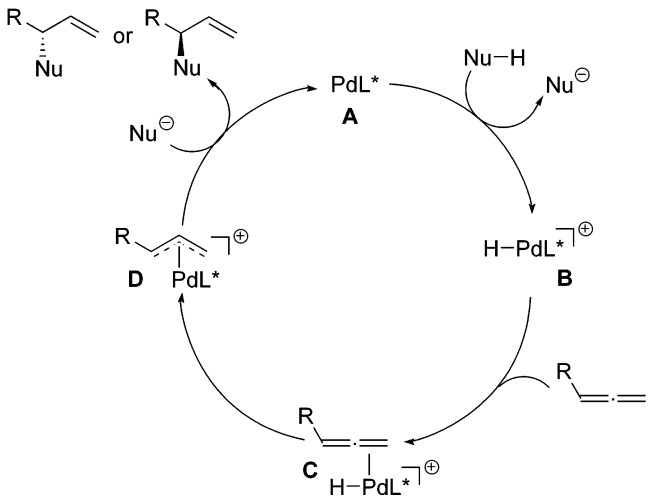
(169)

entry	R	yield [%]	dr (**551**)	*ee* (**551**) [%]
1	Me	85	20 : 1	93
2	Me_2CHCH_2	83	20 : 1	94
3	$H_2C=CHCH_2$	85	20 : 1	90
4	$PhCH_2$	87	16 : 1	93
5	$MeS(CH_2)_3$	67	13 : 1	85



presence of catalytic trifluoroacetic acid and the chiral ligand **552** to yield the α-allylated products **549**, with the highest ee of up to 99% (entry 1). On the other hand, with azalactone **550**, a weaker acid ($pK_a = 9$), a buffer system with K^+tBuO^- and hippuric acid gave the best compromise between yields and ee's (85−94%) of the product **551** in the presence of palladium trifluoroacetate and the chiral ligand **552**. With the benzoic acid/K^+tBuO^- buffer system, the alkylated azalactone **551** (R = Me) was obtained with very good selectivity (24:1 dr) and 98% ee, although in 63% yield. The excellent regio-, diastereo-, and enantioselectivity observed in this reaction makes this process a valuable alternative to aldol-type processes which fail with such stabilized nucleophiles due to unfavorable equilibrium. The proposed catalytic cycle for this novel asymmetric hydrocarbonation is shown in Scheme 15, involving hydropalladation as the initial step.[202]

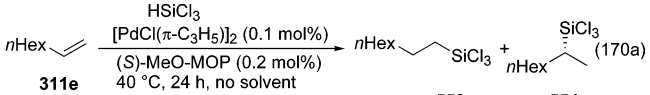
Scheme 15. Proposed Catalytic Cycle for the Asymmetric Hydrocarbonation of Allenes (Eqs 168 and 169)



12. Hydrosilylations

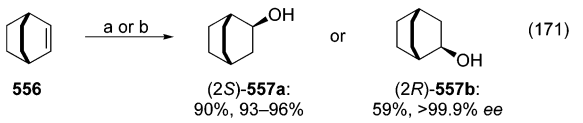
12.1. Hydrosilylation of Alkenes and Alkynes

The catalytic asymmetric hydrosilylation of alkenes is recognized as an important method for the preparation of optically active alcohols by further oxidation of the obtained chiral silanes (eqs 170−172).[203]



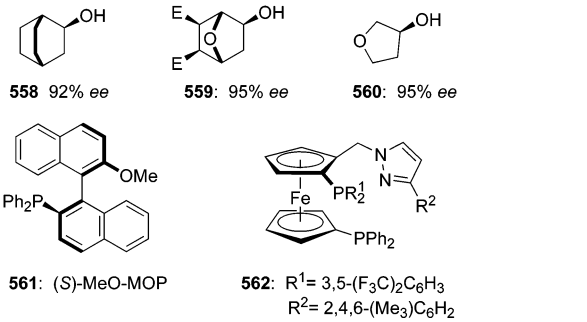
(170a)

(170b)



(171)

a) i) $HSiCl_3$, Pd/(*R*)-MeO-MOP (0.01 mol%), ii) KF, H_2O_2, $KHCO_3$
b) i) $HSiCl_3$, $Pd(COD)Cl_2$ (0.1 mol%), **562**(0.1 mol%), C_6H_6, rt, ii) KF, H_2O_2



Hayashi and co-workers first reported[204] the Pd-catalyzed asymmetric hydrosilylation of olefins and achieved high enantioselectivities (up to 95%) and regioselectivity for the branched terminal olefins using a Pd catalyst with (*S*)-MeO-MOP as chiral ligand (**561**) (eq 170). Similarly, the hydrosilylation−oxidation of norbornene in the presence of the Pd−MeO-MOP catalyst gave the *exo*-(2*S*)-norbornanol **557a** in high yield and ee (93−96%). The use of the chiral ferrocene ligand **562** with bulkier phosphine and pyrazole donor groups gave (2*R*)-norbornanol **557b** in >99.5% ee (eq 171).[205] Bicyclo[2.2.2]octene and 2,5-dihydrofuran derivatives were also successfully subjected to asymmetric hydrosilylation−oxidations under similar conditions with the Pd−(*S*)-

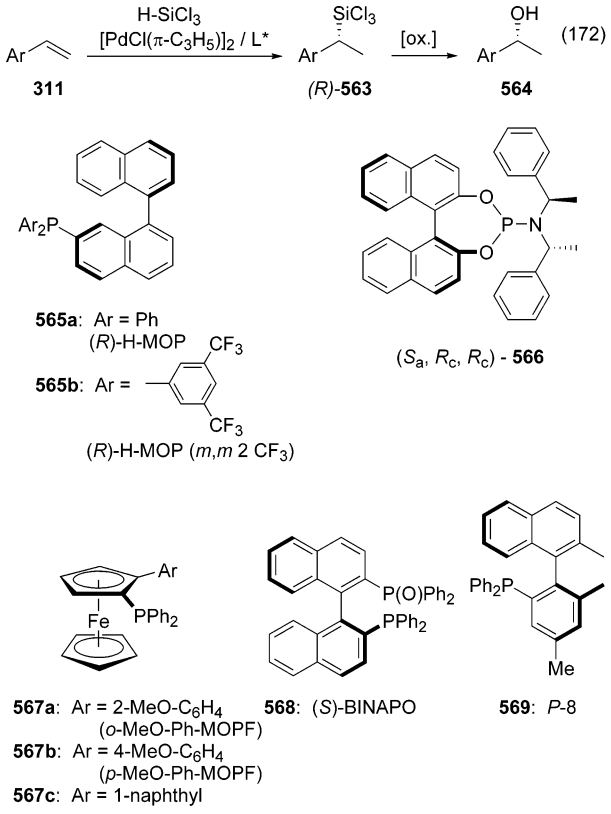
Table 19. Pd-Catalyzed Asymmetric Hydrosilylation of Styrenes in the Presence of Various Chiral Ligands (Eq 172)

entry	Ar	Pd/L* (mol %)	conditions	yield[b] (%)	ee[c] (%)	ref
1	Ph	*ent*-**565b** (0.1/0.2)	0 °C, 12 h	100	93 (*R*)	207
2	Ph	**565b** (0.1/0.2)	0 °C, 12 h	100	93 (*S*)	208
3	Ph	**565b** (0.1/0.2)	−20 °C, 24 h	85	98 (*S*)	208
4	Ph	**566** (0.125/0.5)	20 °C, 16 h	87	99 (*R*)	209
5	Ph	**567b** (0.1/0.2)	rt, 5.5 h	100[d]	90 (*S*)	210
6	4-MeC_6H_4	**565b** (0.1/0.2)	0 °C, 0.5 h	90	95 (*S*) (89)[a]	208
7	3-ClC_6H_4	**565b** (0.1/0.2)	0 °C, 4 h	93	96 (*S*) (95)[a]	208
8	3-ClC_6H_4	**566** (0.125/0.5)	20 °C, 60 h	91	98 (*R*)	209
9	4-$MeOC_6H_4$	**565b** (0.1/0.2)	−10 °C, 20 h	90	97 (*S*) (61)[a]	208
10	4-$CF_3C_6H_4$	*ent*-**565b** (0.1/0.2)	0 °C, 5 d	98	96 (*R*)	207
11	3-$CF_3C_6H_4$	**566** (0.125/0.5)	40 °C, 60 h	88	98 (*R*)	209
12	3-$NO_2C_6H_4$	**565b** (0.1/0.2)	0 °C, 6 d	89	98 (*S*)	208
13	2,4-$(Me)_2C_6H_3$	**566** (0.125/0.5)	20 °C, 40 h	80	96 (*R*)	209

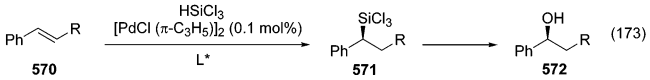
[a] With (*S*)-H-MOP. [b] Isolated yield of silane **563**. [c] ee of **564**. [d] % conversion.

MeO-MOP catalyst to give the optically active alcohols **558**−**560** with ee's up to 95%.[206]

Hayashi and co-workers have also reported the asymmetric hydrosilylation of styrene in the presence of the chiral (*S*)-H-MOP ligand **565a** in high yield and with a maximum ee of 93% (eq 172) (Table 19, entry 1).[207]



In subsequent work, they described the hydrosilylation of styrene using (*R*)-2-bis[3,5-bis(trifluormethyl)phenyl]phosphino-1,1′-binaphthyl **565b**, which gave (*S*)-1-phenylethanol **564** (Ar = Ph) in 98% ee after oxidation of the formed silane **563** (Table 19, entry 3).[208] The Pd complex with ligand **565b** also efficiently catalyzed the asymmetric hydrosilylation of styrenes substituted at the phenyl ring to give the corresponding benzyl alcohols with higher ee's than observed with the H-MOP ligand (entries 6, 7, 9, and 12). The Pd−**565b** complex was also found to be equally effective in the asymmetric hydrosilylation of β-substituted styrenes to give the corresponding higher benzyl alcohols (eq 173, entries 1, 3, and 4)[208] in 97−98% ee.

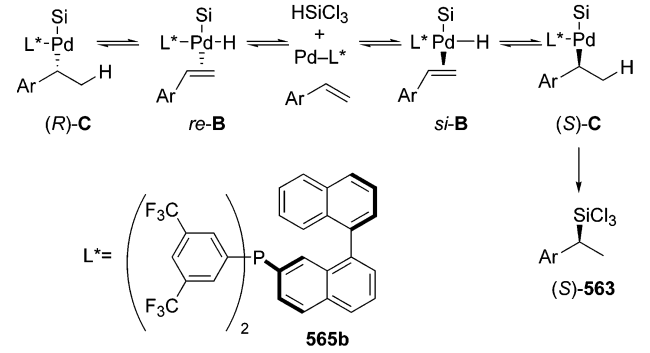


entry	R	Pd / L* [mol%]	conditions	yield **571** [%]	*ee* **572** [%]	Ref.
1	Me	**565b** (0.1 / 0.2)	0 °C, 48 h	81	98 (*S*) (89)[a]	[208]
2	Me	**566** (0.125 / 0.5)	40 °C, 40 h	91	98 (*R*)	[209]
3	CH_2OMe	**565b** (0.1 / 0.2)	0 °C, 30 h	85	97	[208]
4	CH_2OCH_2Ph	**565b** (0.1 / 0.2)	20 °C, 16 h	87	97 (*S*)	[208]

[a] with (*S*)-H-MOP (*ent*-**565b**)

On the basis of deuterium labeling studies of specifically deuterated styrenes, they demonstrated that, using ligand **565b**, the β-hydrogen elimination from the 1-phenylethyl(silyl)palladium intermediate (Scheme 16) is very fast compared to the reductive

Scheme 16. Proposed Mechanism for Hydrosilylation with (*R*)-H-MOP(*m*,*m*-2CF_3) 565b



In subsequent work, they described the hydrosilylation of styrene using (*R*)-2-bis[3,5-bis(trifluormethyl)phenyl]phosphino-1,1′-binaphthyl **565b**, which gave (*S*)-1-phenylethanol **564** (Ar = Ph) in 98% ee after oxidation of the formed silane **563** (Table 19, entry 3).[208] The Pd complex with ligand **565b** also efficiently catalyzed the asymmetric hydrosilylation of styrenes substituted at the phenyl ring to give the corresponding benzyl alcohols with higher ee's than observed with the H-MOP ligand (entries 6, 7, 9, and 12). The Pd−**565b** complex was also found to be elimination, whereas with ligand **565a** the β-hydrogen elimination is slower.

Thus, the higher enantioselectivity employing **565b** can be attributed to the fast β-hydrogen elimination from the alkylpalladium intermediate coordinated with **565b**, followed by a highly selective reductive elimination from one of the diastereomeric intermediates. Thus, the catalytic cycle (Scheme 16) appears to involve both of the diastereomeric alkylpalladium intermediates (*S*)-**C** and (*R*)-**C**, which undergo a fast equilibration by the β-hydrogen elimination and

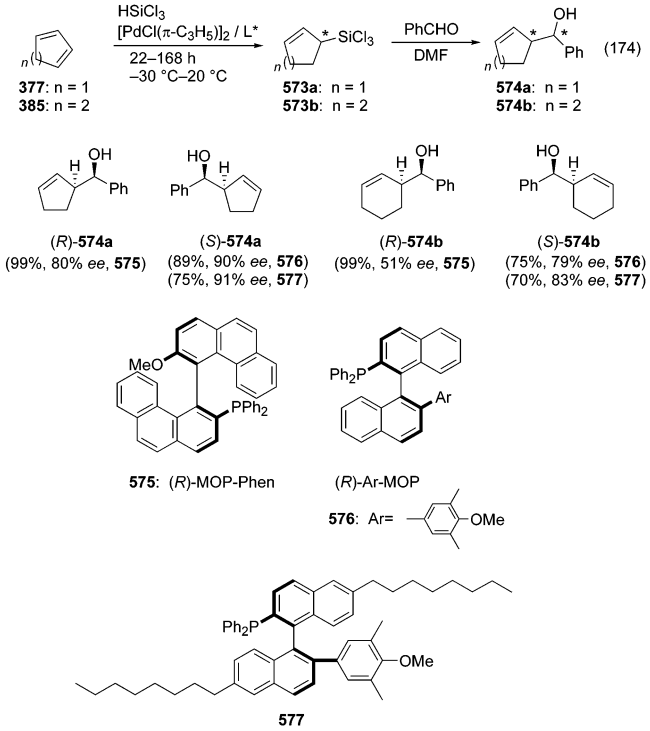
hydropalladation process. Reductive elimination takes place selectively from (*S*)-**C** to give the hydrosilylated product (*S*)-**563**. (*R*)-**C**, which is much less reactive toward reductive elimination, undergoes β-hydrogen elimination to turn back to (*S*)-**C**, resulting in the formation of (*S*)-**563**. However, why the bis(fluoromethylated) H-MOP ligand **565b** causes the fast β-hydrogen elimination, resulting in high enantioselectivity, and which electronic or steric characteristic of **565b** is responsible for it remain to be found out.

Recently, Johannsen and co-workers have demonstrated that the Pd complex with chiral phosphoramidate ligand **566**, with a chiral BINOL structure with an additional chiral element on the amine, is found to be a most efficient catalyst system for the asymmetric hydrosilylation of styrene to yield benzyl alcohol **564** with 99% ee, which is the highest enantioselectivity observed so far for this reaction (Table 19, entry 4).[209] The Pd−**566** catalyst also works efficiently for a variety of substituted styrenes to yield benzyl alcohols with high optical purities (Table 19, entries 8, 11, and 13) (eq 173, entry 2). The same researchers have also recently developed a series of atropisomeric and planar chiral 2-aryl-1-diphenylphosphanylferrocene ligands **567** and examined their efficiency in the asymmetric hydrosilylation of styrene. Employing ligand **567b**, they obtained a maximum ee of 90% (Table 19, entry 5), with an extremely high turnover frequency (TOF) exceeding 180 000/h.[210] Recently, Pd catalysts with chiral ligands such as (*S*)-BINAPO (**568**)[211] and *P*-8 (**569**)[212] have also been examined for the asymmetric hydrosilylation of styrene to afford benzyl alcohols with moderate to good ee's.

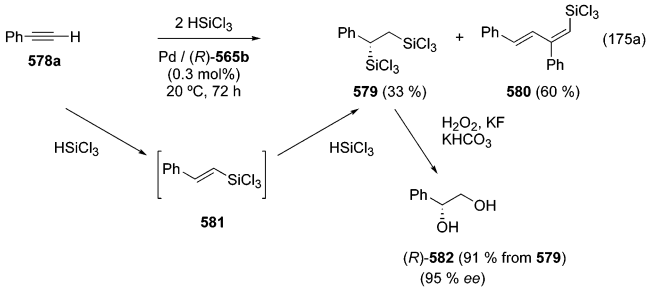
Asymmetric hydrosilylation of 1,3-dienes was investigated earlier employing Pd−chiral ferrocenyl and binaphthyl complexes to give hydrosilylated products with moderate enantioselectivities.[213] Hayashi and co-workers reported significant improvement in the ee's as well as chemical yields in the asymmetric hydrosilylation of cyclic dienes using (*R*)-MOP−Phen ligand **575** to give (*R*)-cyclopentenyl carbinol **574a** from cyclopentadiene with a maximum ee of 80%, whereas with 1,3-cyclohexadiene, only a moderate ee (51%) of the carbinol (*R*)-**574b** was obtained, although in high chemical yield (eq 174).[214]

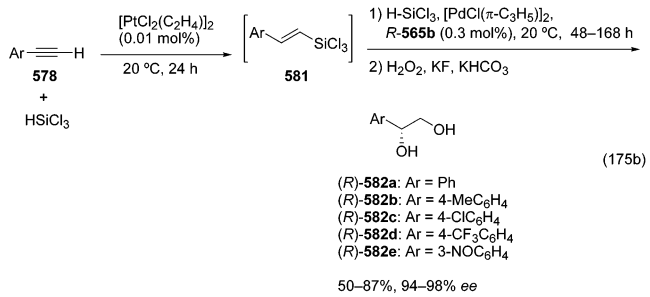
Recently, Hayashi et al. have achieved ee's of up to 90 and 79% for the carbinols (*S*)-**574a** and (*S*)-**574b**, respectively, using 2-(diphenylphosphino)-2′-arylbinaphthyl[(*R*)-Ar-MOP] **576**.[215] Also, they achieved further improvement in ee's, especially for cyclohexyl carbinol **574b** (up to 83%), by using MOP ligand **577**, containing two *n*-octyl groups at the 6 and 6′ positions of the (*R*)-2-(diphenylphosphino)-2′-aryl-1,1′-binaphthyl skeleton,[216] which makes the palladium−phosphine complex soluble in the reaction medium, allowing high catalytic activity at lower reaction temperature (−10 to −30 °C), to give the highest ee's reported to date for the carbinols **574a** (91%) and **574b** (83%).[216]

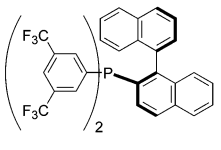
An efficient enantioselective synthesis of 1,2-diols from arylacetylenes by use of enantioselective palladium-catalyzed asymmetric hydrosilylation as a key step has been recently accomplished by Hayashi



and co-workers (eqs 175a,b).[217] Earlier studies employing double hydrosilylation of phenylacetylene using the Pd−(*R*)-MOP(*m*,*m*-2-CF_3) complex **565b** gave 1,2-bis(trichlorosilyl)phenylethane **579** (33%) along with trichlorosilylbutadiene **580** (60%) with low selectivity (eq 175a), although subsequent oxidation of **579** proceeded smoothly to give (*R*)-phenyl-1,2-ethanediol **582** in 91% yield with 95% ee. Subsequently, they developed a high-yielding, one-pot asymmetric double hydrosilylation of arylacetylenes by use of a platinum catalyst for the hydrosilylation



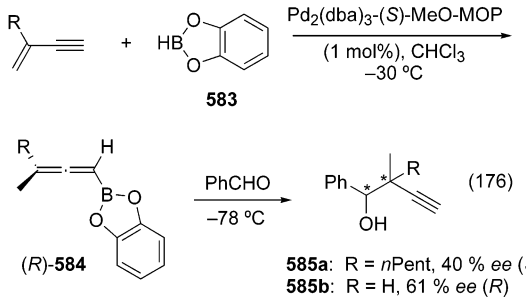




(*R*)-**565b**

as the first step [phenylacetylene → **581**] and then palladium−(*R*)-**565b** catalyst for the second step [**581** → **579**] (eq 175b). Subsequent oxidation of the resulting disilanes (H_2O_2/KF/$KHCO_3$) gave the corresponding 1,2-diols (*R*)-**582** in good yields and excellent ee's of 94−98%.[217]

A report on the Pd-catalyzed asymmetric hydroboration[218] of 1,3-enynes using (*S*)-MeO-MOP phosphine as a ligand has shown the product to be the optically active allenylborane **584**, which reacts with benzaldehyde (with syn attack) to give the optically active carbinol **585b** (R = H) in up to 61% ee (eq 176). Although the enantioselection is not high enough, the reaction provides the first example of an enantioselective synthesis of allenyl boranes **584**.

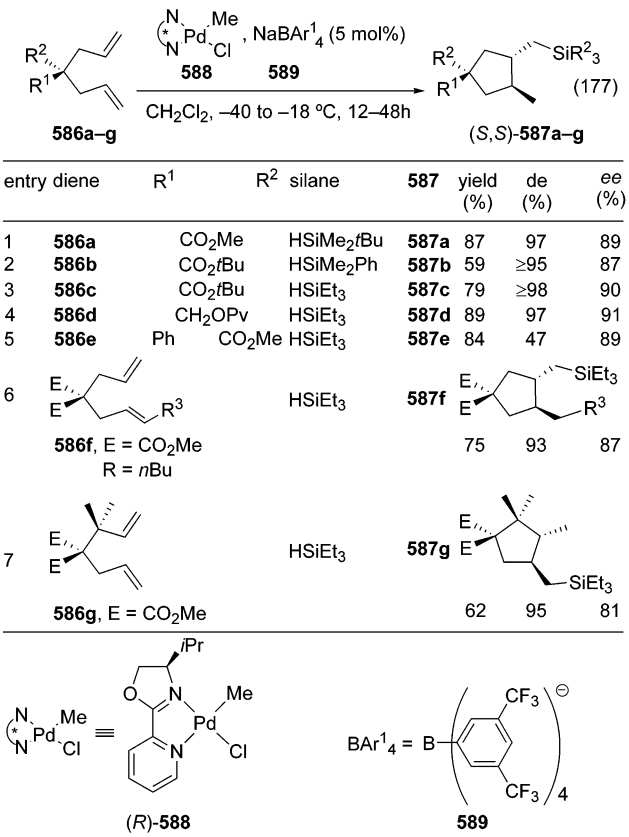


12.2. Cyclization–Hydrosilylation of Functionalized 1,6-Dienes

The cyclization−hydrosilylation of functionalized 1,6- and 1,7-dienes, leading to five- and six-membered carbocycles, has been recently investigated by Widenhoefer and co-workers.[219] In a continuation of these studies, they have described the first example of an asymmetric version of this highly efficient carbocyclization reaction.[220] Thus, for example, using a Pd complex with the pyridine-oxazoline chiral ligand **588**, hydrosilylative cyclization of the dienes **586** proceeded smoothly to afford the five-membered carbocycles **587** with high regio-, diastereo-, and enantioselectivity, to yield only the trans-disubstituted cyclopentanes (eq 177).[220]

This efficient carboannulation protocol consistently produced high levels of diastereo- (>95%) and enantioselectivity (up to 91% ee) with a wide range of substrates and silanes. A variety of substituted silanes, including dimethyl-*tert*-butyl- (entry 1), dimethylphenyl- (entry 2) and triethylsilanes, reacted smoothly with a range of dienes containing diester (entries 1−3 and 7), protected diol (entry 4), and monoester (entry 5) moieties under similar conditions, furnishing substituted five-membered carbocycles in good yields and enantioselectivity. Similarly high yields and good regio- and stereoinduction were obtained for the cyclization products from dienes substituted at the terminal carbon atom (**586f**) or at the allylic carbon atom (**586g**) (entries 6 and 7). A possible transition-state model for the enantiodetermining step in this cyclization reaction, as suggested by Widenhoefer in a subsequent detailed paper,[221] is shown in Scheme 17.

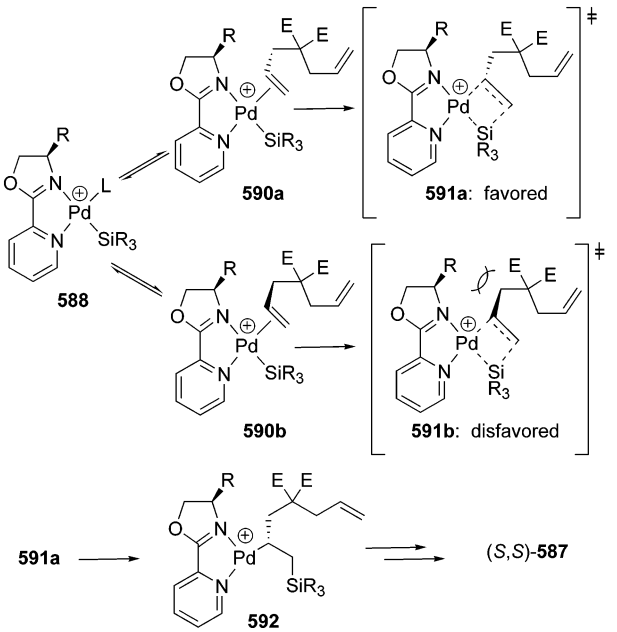
Of the two possible isomeric olefin coordinating Pd complexes (**590a** and **590b**), the intermediate **590a** is expected to undergo a β-migratory insertion of the

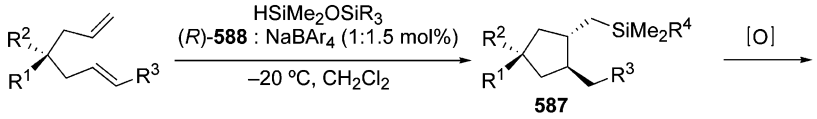


entry	diene	R^1	R^2	silane	587	yield (%)	de (%)	ee (%)
1	**586a**	CO_2Me		$HSiMe_2tBu$	**587a**	87	97	89
2	**586b**	CO_2tBu		$HSiMe_2Ph$	**587b**	59	≥95	87
3	**586c**	CO_2tBu		$HSiEt_3$	**587c**	79	≥98	90
4	**586d**	CH_2OPv		$HSiEt_3$	**587d**	89	97	91
5	**586e**	Ph	CO_2Me	$HSiEt_3$	**587e**	84	47	89
6	**586f**, E = CO_2Me, R = *n*Bu			$HSiEt_3$	**587f**	75	93	87
7	**586g**, E = CO_2Me			$HSiEt_3$	**587g**	62	95	81

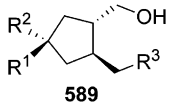
olefinic bond into the Pd−Si bond to give **592** at a higher rate than does **590b**, which is in eqilibrium with **590a** as the substituent (R) at the oxazoline moiety and the substituent at the olefin in **590a** are directed toward opposite faces of the coordinating plane in transition state **591a**. In the transition state **591b**, the substituents are both directed to the same side of the plane, and therefore **591b** has a higher energy. Subsequent transformation of the intermediate **592** then gives (*S*,*S*)-carbocycles **587** (Scheme 17).

Scheme 17. Proposed Mechanism for the Pd-Catalyzed Enantioselective Diene Cyclization/ Hydrosilylation (Eq 177)





586a, $R^1 = R^2 = CO_2Me$, $R^3 = H$
586h, $R^1 = R^2 = CO_2Et$, $R^3 = Me$
586d, $R^1 = R^2 = CH_2OPv$, $R^3 = H$
586i, $R^1 = R^2 = CH_2OBn$, $R^3 = H$
586j, $R^1 = R^2 = CH_2OPv$, $R^3 = Me$
586k, $R^1 = Ph$, $R^2 = CH_2OPv$, $R^3 = H$
586l, $R^1 = R^2 = CO_2Bn$, $R^3 = H$



(178)

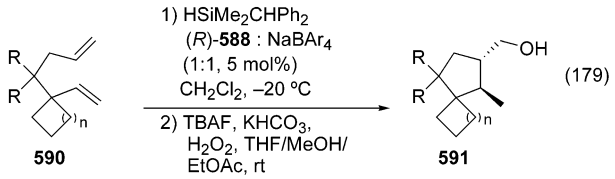
entry	substrate	silane	% yield **587**	% *ee* **587**	% yield **589**	dr %	% *ee* **589**	oxidation method	ref.
1	**586a**	PMDS[a]	95	–	93	–	75 (*S*,*S*)	A	[222]
2	**586a**	$HSiMe_2OTPS$	100	91	48	>50:1	90	D	[223]
3	**586h**	$HSiMe_2CHPh_2$	87	–	76	–	90	B	[224]
4	**586d**	PMDS	98	82	85	>50:1	82	A	[222]
5	**586d**	$HSiMe_2OTPS$	99	95	73	>50:1	95	B	[223, 224]
6	**586d**	$HSiMe_2CHPh_2$	96	–	87	–	95	B	[224]
7	**586i**	$HSiMe_2OTPS$	82	–	76	>50:1	94	C	[224]
8	**586i**	$HSiMe_2CHPh_2$	89	–	73	–	95	B	[224]
9	**586j**	$HSiMe_2OTPS$	92	–	71	39:1	89	B	[224]
10	**586k**	$HSiMe_2OTPS$	90	–	69	1.3:1	92	B	[224]
11	**586l**	$HSiMe_2CHPh_2$	87	–	88	–	94	B	[224]

A KF, AcO_2H, DMF, 25 °C, 48 h; **B** = TBAF, KF, $KHCO_3/H_2O_2$/THF/MeOH, 25 °C, 72 h;
C = TBAF, $KHCO_3/H_2O_2$/THF/MeOH, reflux, 24 h; **D** = 1. TBAF, THF, 2. Ac_2OH, KF, DMF

[a] pentamethyl disiloxane

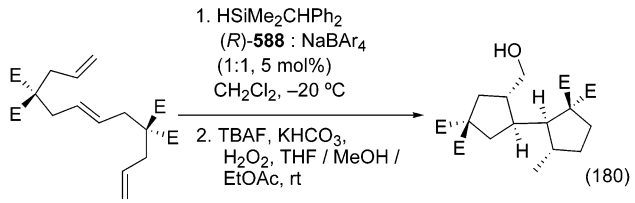
In a subsequent study, Widenhoefer and co-workers also examined the Pd-catalyzed asymmetric diene cyclization−hydrosilylation of a number of 1,6-dienes with functionalized silanes and disiloxanes to form silylated carbocycles, which could be oxidized under mild conditions to the corresponding alcohols (eq 178).[222−224]

Initial studies with PMDS gave silylated products **587** in high yields and ee's (85−91%) which, on oxidation, led to the corresponding alcohols **589**, but with moderate ee's (75−82%) (entries 1 and 4).[222] On the other hand, the reaction of $HSiMe_2OTPS$ with diene **586a**, in the presence of a chiral Pd catalyst derived from **588**, proceeded efficiently to afford the corresponding silylated carbocycles **587a** in excellent yield and high ee.[223] Oxidation of **587a** gave the alcohol **589a** with high ee but in low yield (48%) (entry 2). This could be explained by the observation that the formed silylated carbocycle with two ester groups undergoes dealkoxycarbonylation as a competing pathway in TBAF-mediated oxidation. Thus, oxidation of the carbocycles which do not possess this *gem*-dicarbonyl moiety proceeded smoothly under these conditions (B, C) to give the corresponding alcohols in high yields and ee's (entries 5, 7, 9, and 10).[224] The asymmetric diene cyclization−hydrosilylation−oxidation employing benzhydryldimethylsilane proved to be most efficient and tolerated most of the olefinic, ester, and ether functionalities to yield the corresponding carbinols **589** in high yields and >90% ee (entries 3, 6, 8, and 11).[224] Tolerance of allylic substitution allowed the synthesis of hydroxymethylspirobicycles **591** (eq 179) from **590** using benzhydrylsilane in good yields and high enantioselectivity.



(179)

R	n	yield silylation [%]	yield oxidation [%]	*ee* [%]
CH_2OPv	3	81	71	93
CO_2Et	1	100	82	86
CO_2Et	2	98	98	88



592: E = CO_2Et

(180)

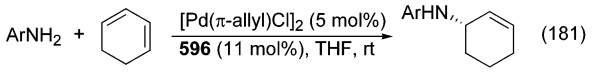
593: 85 %, 66 % *ee*

A similar tolerance of olefinic substitution allowed the asymmetric domino cyclization−hydrosilylation of the triene **592** to form tethered bicyclopentane **593** in high yield, although with diminished enantioselectivity (eq 180) of 66% ee.[224]

13. Hydroamination of 1,3-Dienes

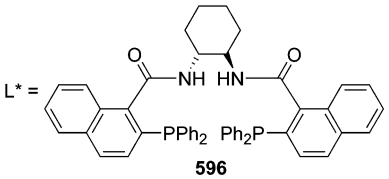
A highly enantioselective palladium-catalyzed hydroamination of cyclic 1,3-dienes[225] has been recently reported by Hartwig and co-workers (eq 181).[226] For its racemic version, they developed use of a high-throughput calorimetric assay to identify the catalysts for the regioselective hydroamination of dienes at room temperature, which showed that the complex

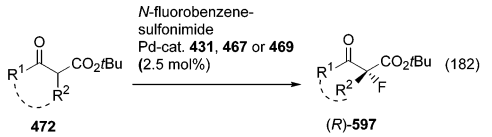
formed from $[Pd(\pi\text{-allyl})Cl]_2$ and PPh_3 in TFA was most active for the regioselective hydroamination of 1,3-cyclohexadiene.[226] Subsequently, for its enantioselective version, optimization of the reaction with various chiral ligands and reaction conditions demonstrated that the modified Trost ligand **596** provided the best combination of yield and enantioselectivity for a broad range of arylamines (eq 181) to give **595** with the highest ee of 95% (entries 5 and 6). Applying the same conditions to the reaction of cycloheptadiene gave the 1,4-addition product in 22% yield with 66% ee.[226]



entry	amine	time [h]	yield [%]	*ee* [%]
1[a]	$PhNH_2$ (**594a**)	72	61	91 (*S*)
2	$PhNH_2$ (**594a**)	120	87	89 (*S*)
3	$4\text{-}MeC_6H_4NH_2$ (**594b**)	120	78	86 (*S*)
4	$2\text{-}MeC_6H_4NH_2$ (**594c**)	120	59	90 (*S*)
5	$4\text{-}EtO_2CC_6H_4NH_2$ (**594d**)	120	83	95 (*S*)
6	$4\text{-}F_3CC_6H_4NH_2$ (**594e**)	120	73	95 (*S*)

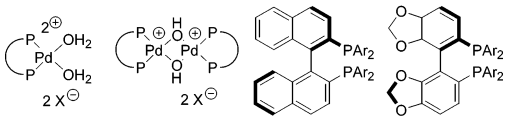
[a] Pd catalyst (2.5 mol%), **596** (5 mol%)





entry	ketoester	catalyst	Temp [°C]	time [h]	yield [%]	*ee* [%]
1	**472a**: n = 1	**467d** (TfO)	20	18	73	92
2[a]	**472a**: n = 1	**467d** (TfO)	20	18	90	92
3	**472b**: n = 2	**467c** (BF_4)	–10	20	91	94
4	**472c**	**467c** (TfO)	–20	36	85	83 (*R*)
5	**472d**: $R^1 = R^2 = CH_3$	**467d** (TfO)	20	72	49	91
6	**472f**: R^1 = Ph, $R^2 = CH_3$	**431c** (BF_4)	20	40	92	91 (*R*)
7[b]	**472f**: R^1 = Ph, $R^2 = CH_3$	**469c** (TfO)	20	48	96	91
8	**472g**: $R^1 = CH_3$, R^2 = Et	**467c** (TfO)	20	42	88	87

[a] *i*PrOH as solvent; [b] 1 g scale



431 (BF_4) **467** (TfO) **a**,**c** **d**
469 (TfO)

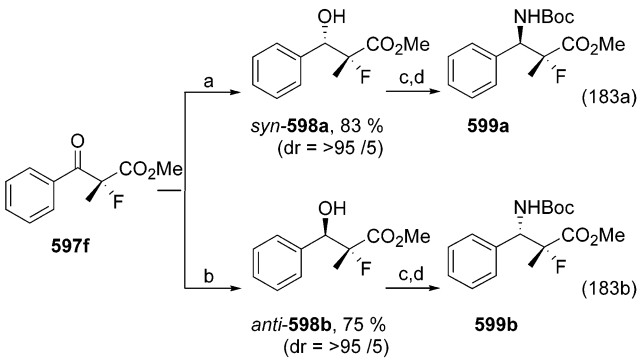
a: Ar = Ph, (*R*)-BINAP
c: Ar = 3,5-dimethylphenyl : (*R*)-DM-BINAP
d: Ar = 3,5-di(*t*butyl)-methoxyphenyl (*R*)-DTBM-SEGPHOS

14. Fluorination of β-Ketoesters

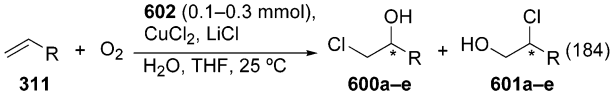
Development of efficient methods for direct enantioselective construction of fluorinated stereogenic carbon centers is of high interest[227] due to the importance of organofluorine compounds in medicinal chemistry. Only a few examples of catalytic asymmetric fluorinations of *β*-ketoesters using either chiral Ti catalysts[228] or cinchonine-derived quaternary salts[229] are known in the literature, and new efficient catalytic systems displaying high selectivity for this reaction are very much desired. Recently, Sodeoka and co-workers[230] have developed a highly efficient catalytic enantioselective fluorination reaction of various *β*-ketoesters using the chiral palladium hydroxy complexes **431** or **449** earlier employed for enantioselective Michael addition of *β*-ketoesters (eq 182).

N-Fluorobenzenesulfonimide (NFSI) was found to be the most effective fluorinating agent for this reaction. Earlier studies using (*R*)-BINAP catalysts (**469a** and **449a**) gave fluorinated cyclopentane carboxylate **597a** in good yield and 79% ee. However, when meta-substituted aryl BINAPs such as (*R*)-DM-BINAP(**467c**) or (*R*)-DTBM-SEGPHOS (**467d**) were employed, ee's could be improved to 92% (entries 1 and 2). Interestingly, the use of ethanol as solvent dramatically accelerated the reaction (entry 1), and the chemical yield of **597a** could be increased to 90% in 2-propanol (entry 2). The fluorination of cyclohexane carboxylate **472b** afforded the α-fluorinated product **597b** under identical conditions, with the highest ee of 94% in 91% yield (entry 3), whereas the indane-2-carboxylate **472c** afforded the fluorinated product **597c** in 83% ee (entry 4). The reaction of acyclic *β*-ketoesters **472d**,**f**,**g**,**h** also gave the fluorinated esters with excellent enantioselectivities (87−91% ee, entries 5−8). In one example, the reaction could be easily scaled up (1 g of **472g**) without any loss of reaction efficiency (entry 7).

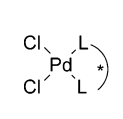
The fluorinated *β*-ketoester **597h** based on **597f** was also transformed in three steps into both diastereoisomers of α-fluorinated *β*-hydroxy and *β*-amino acid derivatives (eqs 183a,b) in a highly diastereoselective manner; thus demonstrating the further utility of this method for synthesis of biologically important optically active compounds.[230]



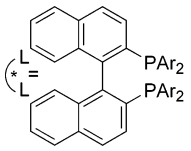
a) $PhMe_2SiH$, TBAF, DMF; b) Ph_3SiH, TFA; c) DEAD, Ph_3P, DPPA, THF, 79 % from *syn*-**598a**, 73 % from *anti*-**598b**; d) Pd/C, H_2, $(Boc)_2O$, MeOH, 80 % for *anti*-**599a**; 57 % for *syn*-**599b**

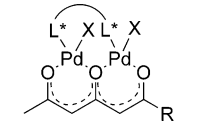


entry	substrate R	catalyst	ratio 600/601	*ee* [%]	TON
1	Me (**311b**)	**602a**	3.5	94 (*S*)	195
2	*n*Bu (**311e**)	**602b**	4.0	81	200
3	*n*Pent (**311f**)	**602b**	18.7	87	155
4	CH_2OPh (**311g**)	**602b**	>95	93	170
5	CH_2O(1-naphth) (**311h**)	**602b**	>95	80	175

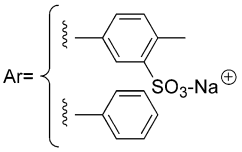


430c
monometallic



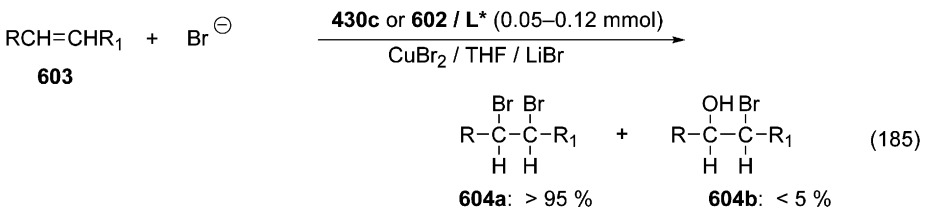


bimetallic **602a**: R = Me
602b: R = Ph

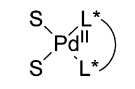


15. Wacker-Type Oxidation and Oxidative Cyclization

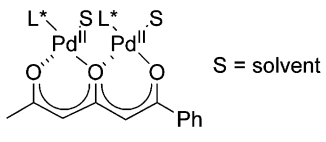
The formation of chlorohydrins has been observed to an appreciable extent in Pd^{II} chloride-mediated Wacker oxidations of alkenes under high Cl^- and $CuCl_2$ concentration.[231] Moreover, Henry and co-workers showed in earlier studies that the substitution of chloride by pyridine in the coordination sphere of $PdCl_4^{2-}$, to give $[PdCl_3(py)^-]$, resulted in the formation of chlorohydrins at a very low concentration of Cl^- (0.2 *m*),[232] which opens up the way for the Pd-catalyzed asymmetric synthesis of chlorohydrins from α-olefins using chiral ligands. However, the use of chiral amine ligands provided the chlorohydrins in very low optical purity (10−15% ee), whereas neutral monometallic Pd^{II} complexes containing a chiral diphosphine ligand (BINAP) were found to be insoluble in the reaction medium.[232] In a recent study, Henry and co-workers[233] have found a solution for this problem by using either monometallic Pd^{II} complexes **430c** with sulfonated phosphine ligands or new homobimetalated complexes of type **602** with



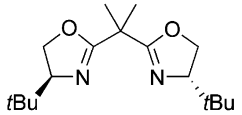
entry	substrate	L*-L*	LiBr [M]	catalyst	yield [%]	*ee* [%] **602a**	catalyst turnover
	ArO						
1	Ar = 4-$MeOC_6H_4$	(*S*)-BINAP	0.25	**602**	95	96	85
2	Ar = 4-CNC_6H_4	(*S*)-Tol-BINAP	0.13	**602**	95	97	88
3	Ar = Ph	(*S*)-BINAP	0.20	**602**	95	95	148
4	Ar = (2,6-di-^{i}Pr)C_6H_3	(*S*)-BINAP	0.20	**430d**	95	94	80
5	CO_2Me	(*S*)-METBOX	0.20	**602**	84	94	25
6	CO_2Me	(*S*)-METBOX	0.30	**430d**	80	82	30 (*RS*,*SR*)
7	Ph, OH	(R)-BINDA	0.20	**602**	77	80	21 (*RS*,*SR*)
8	Ph, OH	(R)-BINDA	0.00	**602**	75	34	–
9	Ph, CO_2Me	(R)-BINDA	0.20	**602**	84	14	10 (*RS*,*SR*)



430d
monometallic

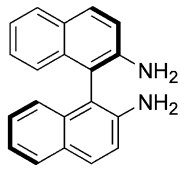


602



605: (*S*)-METBOX

= L* =



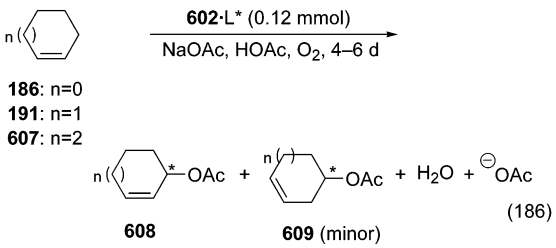
606: (*R*)-BINDA

bridging diphosphanes prepared from $[Pd(MeCN)_4]$-BF_4 by treatment with 1,3,5-pentanetriones and chiral diphosphine ligands such as (*R*)-BINAP. The enantioselectivity using monometalated sulfonated chiral phosphane ligands **430c** was found to be moderate (46−76% ee), with a turnover number of 60−72. However, with the bimetallic chiral catalysts **602**, the oxidation of unsymmetrical olefins gave the chlorohydrins **600a**−**e** with high asymmetric induction of up to 94% ee, along with higher turnover numbers (eq 184).

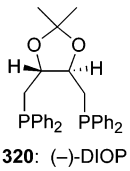
These bimetallic catalysts **602** are found to be most promising for the asymmetric synthesis of chlorohydrins, since in addition to high ee's and turnover numbers, also a high regioselectivity (>95:5) was observed with olefins being *O*-substituted at the allylic position (entries 4 and 5, eq 184).

Henry and co-workers have also reported the Pd^{II}-catalyzed asymmetric synthesis of dibromo compounds using monometallic or bimetallic catalysts containing chiral chelating diphosphine or diamine ligands.[234] Unexpectedly, the treatment of olefins with bromide did not produce the corresponding bromohydrin **604b** but predominantly the dibromides **604a**, which were formed in high enantioselectivity with up to 97% ee (eq 185).

Both mono- and dimetallic catalysts were found to be equally effective. The enantioselectivities for the internal olefins were somewhat poorer than those found for monosubstituted olefins (entries 6−9). Thus, the ee decreased from 94% ee for the bromine addition of methyl acrylate to 82% ee for that of methyl crotonate (entry 5 vs entry 6) employing the same chiral ligand. Also, in the absence of extra bromide ions (LiBr), the ee drops from 80 to 34%, thus demonstrating the importance of the bromide concentration (entry 7 vs entry 8). In addition, Henry and co-workers have also shown that bimetallic Pd^{II} complexes containing a triketone ligand and a bridging DIOP or METBOX ligand oxidize cyclic olefins such as cyclohexene and cyclopentene to give the corresponding allylic acetates in high yields with enantiomeric excess ranging between 52 and 78% (eq 186).[235]

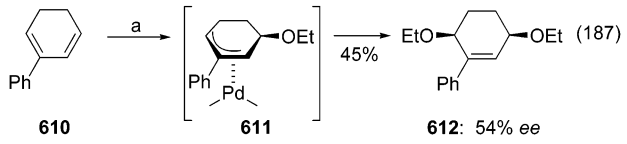


608a: n = 1, 95 %, 52 % *ee* (with (–)-DIOP)
608a: n = 1, 90 %, > 55 % *ee* (with (*S*)-METBOX)
608b: n = 0, 92 %, 78 % *ee* (with (–)-DIOP)
608c: n = 2, 85 %, 70 % *ee* (with (*S*)-METBOX)



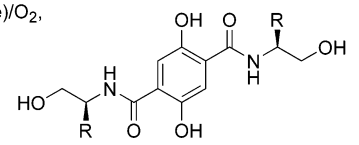
320: (–)-DIOP

The Pd^{II}-catalyzed enantioselective 1,4-dialkoxylation of 2-phenyl-1,3-cyclohexadiene has been recently investigated by Bäckvall and co-workers[236] using the chiral C_2-symmetric 2,5-bisamide hydroquinone ligand **613** (R = Me, *i*Pr, *t*Bu) with a β-amino alcohol moiety to yield 2-phenyl-1,4-diethoxycyclohexene **612** with only moderate yields and ee's (eq 187). These authors have further demonstrated that



610 **611** **612**: 54% *ee*

a) $Pd(OAc)_2$ (10 mol%), **613** (10 mol%), $MeSO_3H$, Fe(phtalocyanine)/O_2, EtOH, CH_2Cl_2



613: R = *i*Pr

the asymmetric induction for the Pd^{II}-catalyzed 1,4-dialkoxylation can be achieved only by the use of ligands with appropriately placed hemilabile groups and that such stereocontrol has not yet been exploited extensively in asymmetric catalytic processes.[237]

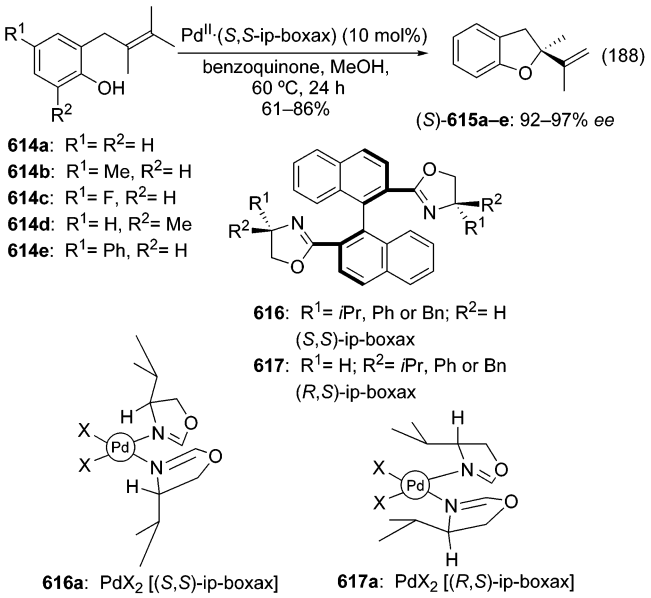
In their pioneering work on intramolecular Wacker-type oxidations, Murahashi and co-workers[238] have demonstrated the oxidative cyclization of *o*-allylphenols catalyzed by a chiral π-allylpalladium complex in the presence of cupric acetate under oxygen atmosphere, affording optically active dihydrobenzofurans, although in low ee's. The reaction was revisited recently by Hayashi and co-workers,[239] who have shown that high enantioselectivity (up to 97%) could be obtained in the Wacker-type cyclization of *o*-allylphenols by use of Pd^{II} catalysts such as **616** (R^1 = *i*Pr, Ph, Bn; R^2 = H) coordinated with chiral bis(oxazoline) ligands based on the 1,1′-binaphthyl backbone. The corresponding binaphthyldiphosphane catalyst could not be used because of its ready oxidation under reaction conditions. The combination of palladium bis(trifluoroacetate), (*S*,*S*)-2,2′-bis[4-isopropyloxazolyl]-1,1′-binaphthyl (*S*,*S*)-ip-boxax **616** (having both the central chirality at the oxazoline moiety and the axial chirality of the binaphthyl residue) in the presence of an excess of benzoquinone was found to be a new efficient catalyst for the cyclization of 2-(2,3-dimethyl-2-butenyl)phenols such as **614a** to afford the corresponding dihydrobenzofuran **615a** in 75% yield with 96% ee (Table 20, entry 2). On the other hand, the palladium catalyst of the diastereomer, (*R*,*S*)-ip-boxax **617**, was found to be much less active and enantioselective (3% yield, 18% ee). The substituted *o*-allylphenols **614b**−**e** also underwent facile asymmetric cyclization under similar conditions using the (*S*,*S*)-ip-boxax−Pd^{II} catalyst system to give the corresponding 2,3-dihydrobenzofurans **615b**−**e** with 92−97% ee's in high yields (eq 188).

The chemical yield and the enantiomeric purity of the product **615a** are found to be strongly affected by the anionic part of the catalyst (Table 20). Thus,

Table 20. Enantioselective Wacker-Type Cyclization of 614a with Cationic Palladium(II)/(*S,S*)-ip-boxax Complexes (Eq 188)

entry	Pd catalyst	Pd/**616** (mol %/mol %)	time (h)	yield **615a** (%)	ee (%)
1	$Pd(OCOCH_3)_2$−(*S,S*)-ip-boxax	10/10	24	44	54 (*S*)
2	$Pd(OCOCF_3)_2$−(*S,S*)-ip-boxax	10/10	24	75	96 (*S*)
3	$Pd(MeCN)_4(BF_4)_2$−(*S,S*)-ip-boxax	10/20	0.8	91	97 (*S*)
4	$PdCl_2$−(*S,S*)-ip-boxax−$2AgBF_4$	10/20	1	91	98 (*S*)
5	$PdCl_2$−(*S,S*)-ip-boxax−$2AgPF_6$	10/20	1	87	95 (*S*)
6	$PdCl_2$−(*S,S*)-ip-boxax−2 $AgSbF_4$	10/20	1	86	97 (*S*)
7[a]	$Pd(OCOCH_3)_2$−(*S,S*)-ip-boxax	1/2	5	75	94 (*S*)

[a] Under reflux.



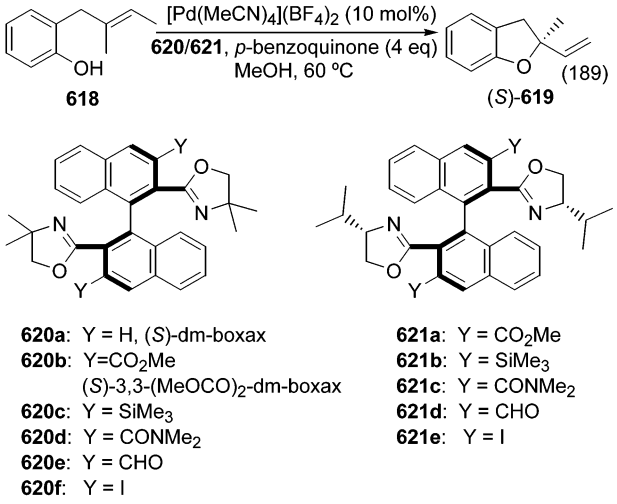
a catalyst system generated from dichlorobis(acetonitrile)palladium and (*S,S*)-ip-boxax did not catalyze the cyclization of **614a**, and the catalyst from palladium diacetate gave only 54% ee of (*S*)-**615a** in 44% yield (entry 1). The trifluoroacetate anion is considered to play a key role in the activation of the coordinated olefin, and it is suggested that a cationic palladium/boxax complex is generated as the active species by the dissociation of the relatively stable trifluoroacetate anion from the palladium complex in a polar solvent like methanol. In a subsequent detailed paper,[240] Hayashi and co-workers have shown that a dicationic palladium(II)/boxax species generated by addition of (*S,S*)-ip-boxax **616** to $Pd(MeCN)_4(BF_4)_2$ was found to be catalytically much more active than $Pd(CF_3CO_2)_2$−(*S,S*)-ip-boxax for the present reaction, yielding **615a** within 50 min in 91% yield with 97% enantiomeric purity (Table 20, entry 3). Essentially the same catalytic activity and enantioselectivity were observed for the formation of **615a** from **614a**, when the dicationic species was generated by an abstraction of chloride from $PdCl_2$−(*S,S*)-ip-boxax by various silver(I) salts such as $Ag(BF_4)$, $AgPF_6$, and $AgSbF_6$ (Table 20, entries 4−6). Furthermore, the amount of the cationic catalyst could be reduced to 1 or 2 mol % under oxygen atmosphere and refluxing methanol to afford **615a** in 75% yield with similar ee's (94%) (entry 7). On the basis of the X-ray structures of (*S,S*)-**616**, it was shown that the isopropyl substituents are located above and below the coordination plane of the Pd complex **617**, as

Table 21. Pd-Catalyzed Wacker-Type Cyclization of *o*-Allylphenol 618 (Eq 189)

entry	substrate	L* (equiv relative to Pd)	temp/time (°C/h)	product	yield (%)	ee (%)
1	**618**	**616** (2.0)	60/0.5	**619**	90	9 (*S*)
2	**618**	**620b** (2.0)	20/2	**619**	90	88 (*S*)
3	**618**	**620a** (2.0)	60/2	**619**	44	38 (*S*)
4	**618**	**620b** (3.0)	20/12	**619**	80	96 (*S*)
5	**618**	**621b** (2.0)	60/24	**619**	63	13 (*S*)
6	**614a**	**620b** (2.0)	60/24	**615a**	30	4 (*R*)

depicted in **616a**. In contrast, in (*R,S*)-**617**, the coordination of the olefin is probably disturbed by the two *i*Pr groups, which results in its low catalytic activity.

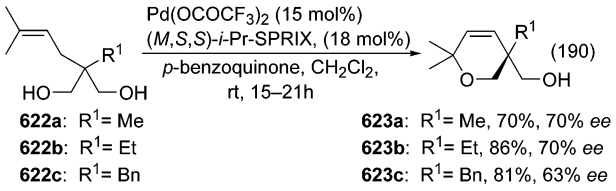
$[Pd(MeCN)_4](BF_4)^2$−(*S,S*)-ip-boxax was not found to be an effective catalyst for the enantioselective cyclization of (*E*)-2-(2-methyl-2-butenyl)phenol **618** and gave the product **619** with very low ee (9%), although in high yield (eq 189) (Table 21, entry 1).

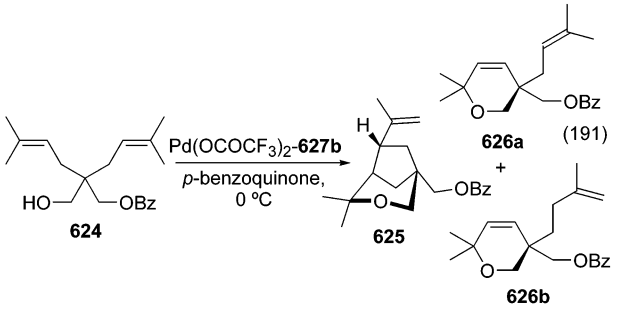


In another paper, Hayashi and co-workers[241] have described the synthesis of a series of novel 2,2′-bis(oxazolyl)-1,1′-binaphthyls **620a**−**f** with various substituents at the C-3 and C-3′ positions and have further shown that the $Pd(MeCN)_4(BF_4)_2$ catalyst with the chiral ligand (*S*)-3,3′-bis(methoxycarbonyl)-dm-boxax **620b** yielded (*S*)-**619** from **618** with ee's as high as 88 and 96%, depending on the ligand/Pd molar ratio (Table 21, entries 2 and 4). On the other hand, the Pd complexes with the corresponding 3,3′-unsubstituted ligand **620a** displayed a lower catalytic activity to give **619** in 44% yield with only 38% ee (entry 3). Similarly, the boxax derivative **621b**,

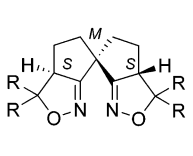
having both (*S*)-isopropyl substituents at the oxazoline ring along with the methoxycarbonyl groups at C-3 and C-3′ positions, gave (*R*)-**619** with only 13% ee (entry 5). It is also noteworthy that ligand **620b** shows only a low asymmetric induction in the cyclization of the tetrasubstituted substrate **614a** to give **615a** (entry 6). This clearly shows that it is difficult to find a general catalyst.

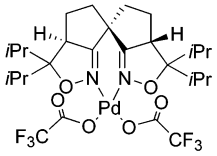
The first report on a catalytic asymmetric Wacker-type cyclization of alkenyl alcohols of type **622** was published recently by Sasai and co-workers.[242] They observed that a catalyst based on (*M*,*S*,*S*)-*i*Pr-SPRIX **627b** and $Pd(CF_3CO_2)_2$ promoted the Wacker-type cyclization of the alkenyl alcohol **622a** in the presence of *p*-benzoquinone to give the 6-*endo* cyclized product **623a** in high yield and up to 70% ee (eq 190).





entry	cat. [mol%]	solvent	time [h]	yield [%]	product ratio (*ee*) [%] 625	626a	626b
1	20	CH_2Cl_2	85	96	68 (95)	5 (45)	27 (60)
2	20	MeOH	24	95	83 (68)	5 (26)	12 (31)
3	10	CH_2Cl_2/MeOH (1:1)	24	99	89 (82)	3 (36)	8 (57)



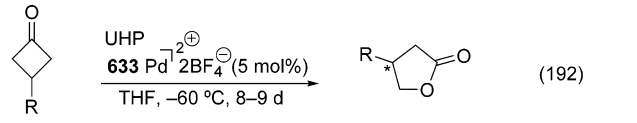


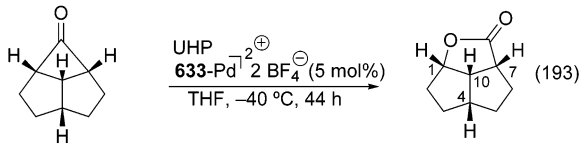
627a: R = H (*M*,*S*,*S*)-H-SPRIX
627b: R = *i*Pr (*M*,*S*,*S*)-*i*Pr-SPRIX
627c: R = Me
627d: R = Et

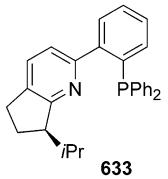
628

The use of known chiral catalysts such as $Pd(CF_3CO_2)_2$−(*S*,*S*)-ip-boxax, BINAP, or bis(oxazolinyl)propane did not promote the reaction of **622a** to give **623a**. X-ray analysis of the single crystal of complex Pd−**627b** revealed that **627b** is coordinated to Pd through the two nitrogen atoms, as depicted in **628**. In the same paper,[242] a highly efficient enantioselective Pd-catalyzed asymmetric domino cyclization employing the dialkyl carbinol substrate **624** has been described to give the bicyclic compound **625** as a single diastereomer (95% ee), along with the dihydropyrans **626a** and **626b**. The latter are formed by a β-elimination of the common intermediate (eq 191, entry 1). The use of methanol as a solvent increased the amount of the bicyclic product **625** but with decreased ee (68%, entry 2), while the mixed CH_2Cl_2/MeOH solvent balanced the yield and the ee with 10 mol % of catalyst (entry 3). A plausible mechanism for this unprecedented reaction involving a domino oxy- and carbopalladation process has also been suggested by these workers.

The first successful example of an enantioselective Baeyer−Villiger oxidation catalyzed by a chiral Pd^{II} complex has been recently reported by Ito and Katsuki (eq 192).[243] The chiral 2-(phosphinophenyl)-







633

pyridine **633** was shown to be an effective ligand for the Pd-catalyzed oxidation of achiral 3-substituted cyclobutanones **629a**−**d** in the presence of the urea−hydrogen peroxide adduct (UHP) as the oxidant to yield the corresponding γ-butyrolactones **630a**−**d** in 60−83% ee (eq 192), with the lowest ee value of 60% obtained with the 3-octylbutyrolactone **630d**. Interestingly, for the oxidation of the tricyclic cyclobutanone **631** under identical conditions, an excellent enantioselectivity of >99% ee for the tricyclic lactone **632** was observed. The reaction has been proposed to proceed via a Pd^{II}−Criegee adduct complex[244] possessing a square planar coordination.

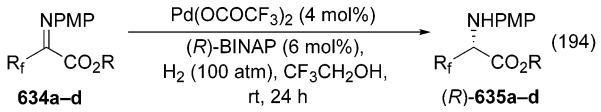
16. Hydrogenation of Imines

The transition metal-catalyzed asymmetric hydrogenation of ketimines is an important method[245,246] in the synthesis of chiral amines also in industrial processes. Recently, a novel highly efficient approach for catalytic asymmetric synthesis of fluoroamino acids[246] has been developed, involving the asymmetric hydrogenation of α-fluorinated iminoesters **634** using a palladium trifluoroacetate−(*R*)-BINAP catalyst (eq 193). In ordinary solvents (toluene, AcOH, *i*PrOH, MeOH, EtOH), only low to moderate ee's and yields of α-aminoesters **635** as the products were obtained. However, both the yields and ee's were dramatically improved by employing fluorinated alcohols such as CF_3CH_2OH, giving maximum ee's of up to 88% (Table 22, entry 1), which was further increased by the addition of an electrolyte (entry 2).

Table 22. Enantioselective Hydrogenation of α-Fluorinated Iminoesters 634 in Trifluoroethanol (Eq 194)

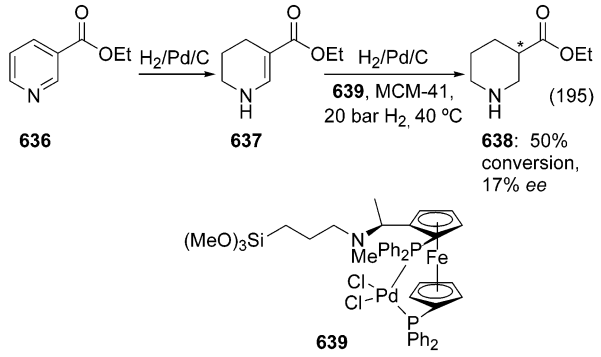
entry	substrate	R_f	R	product	yield **635** (%)	ee (%)
1	**634a**	CF_3	Et	**635a**	>99	88 (*R*)
2[a]	**634a**	CF_3	Et	**635a**	84	91 (*R*)
3[b]	**634a**	CF_3	Et	**635a**	94	88 (*R*)
4	**634b**	CF_3	*t*Bu	**635b**	92	85 (*R*)
5	**634c**	CF_3	Bn	**635c**	95	84 (*R*)
6	**634d**	$CClF_2$	*t*Bu	**635d**	69	81 (*R*)

[a] In the presence of the electrolyte, nBu_4NHSO_4. [b] In $CF_3CF_2CH_2OH$.



Comparable yields and ee's were also obtained using pentafluoropropanol as solvent (entry 3). It has been suggested that the trifluoroethanol preferably coordinates weakly to palladium and thus can easily be replaced by less coordinative fluorinated imines **634**. Alternatively, trifluoroethanol also might influence the chemical character of the imino group by protonation or H-bonding.[247]

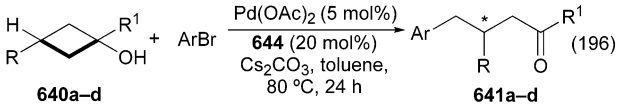
Recently Thomas et al.[248] have developed a new approach for the enantioselective hydrogenation of ethyl nicotinate to give ethyl pipecolinate **638** using a heterogeneous Pd catalyst **639** derived from a 1,1′-bis(diphenylphosphino)ferrocene ligand tethered to the inner wall of a mesoporous silane inorganic support. However, the yield and the ee of product **638** were low (eq 195) and comparable to results reported earlier by Blaser,[249] obtained by using Pd on charcoal in the presence of cinchonidine.



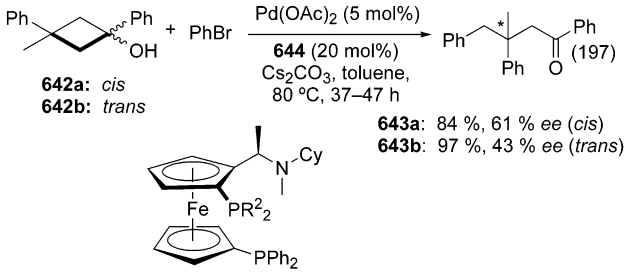
17. Miscellaneous Transformations

Although a selective metal-catalyzed C−C bond cleavage reaction has been reported recently,[250] examples of enantioselective C−C bond cleavage reactions have been scarce in the literature.[251] Uemura and co-workers have recently demonstrated[252] a palladium-catalyzed asymmetric arylation of achiral 3-substituted *tert*-cyclobutanols **640** in an enantioselective C−C bond cleavage to give the chiral ketones **641a**−**d** in high yields with moderate to good enantiomeric excess (eqs 196 and 197).

The chiral ligand (*R*)-*N*-methylcyclohexylamino-1-[((*S*)-2-diphenylphosphino)ferrocenyl]ethylamine (**644**) was found to display the best selectivity using aryl



entry	**640**	R	R^1	Ar	% yield	% *ee*
1	**640a**	Ph	Ph	Ph	83	78
2	**640a**	Ph	Ph	4-ClC_6H_4	90	73
3	**640a**	Ph	Ph	4-MeC_6H_4	91	75
4	**640b**	C_6H_{13}	Ph	Ph	99	64
5	**640c**	*t*Bu	Ph	2-naphth	92	60
6	**640d**	Ph	*n*Bu	Ph	86	60



(*R*)-(*S*)-**644**

bromides as arylating agents. The corresponding γ-arylated ketones **641a**−**d** were obtained with a maximum ee of 78%. The arylation could be applied to 1-aryl- and also 1-alkyl-substituted cyclobutanols (entries 1−5), respectively, to give alkyl−aryl and dialkyl ketones **641a**−**c** and **641d** in high yield but with only moderate enantioselectivity (entry 6). Similarly, the 3-disubstituted cyclobutanols **642a**,**b** gave the corresponding ketones **643a**,**b** having a chiral quaternary center in high yields but again moderate enantioselectivities (eq 197). These results suggest that the enantioselective C−C bond cleavage preferentially occurs at the C−C bond adjacent to the ligand-ligated palladium(II) alcoholate. However, further mechanistic studies and better catalytic systems for this reaction are desired.

18. Conclusion

Pd-catalyzed transformations belong to the most important methods for C−C, C−N, and C−O bond formation. They are mild and tolerate many functional groups. Moreover, they are environmentally benign processes. Thus, in terms of their synthetic importance, especially in the synthesis of complex natural products, they can be compared with aldol and pericyclic reactions. Furthermore, they allow the formation of stereogenic centers and chiral axes with excellent enantioselectivity using chiral ligands.

This review has clearly demonstrated that there is no field where enantioselective Pd catalysis cannot be employed. Even a rather unusual enantioselective C−C bond cleavage could be performed using a Pd catalyst. A disadvantage of enantioselective Pd-catalyzed transformations is the high price of Pd and the usually small turnover numbers, which makes the processes too expensive for industrial use. However, from this review it can also be seen that novel ligands can be developed which allow the use of chiral Pd catalysts with a turnover number of 10^{10}, although up to now with only low enantioselectivity. However,

one can expect that, in the near future, highly potent Pd catalysts for a broad range of enantioselective transformations will be designed which are also suitable for the chemical industry.

19. Addendum

Several interesting publications on Pd-catalyzed enantioselective transformations appeared after the initial submission of this article. In one review, the synthesis and application of optically active bis(oxazolinyl)phenyl (Phebox) as an anionic N−C−N pincer ligand were described.[253] In another review,[254] enantioselective hydrovinylation reactions of alkenes are discussed, and in a third review,[255] an overview of transition metal-catalyzed enantioselective ring-opening reactions of oxabicyclic alkenes is presented.

Dong and co-workers[256] used efficiently novel planar chiral diphosphine-oxazoline ferrocenyl ligands in the Pd-catalyzed asymmetric intermolecular Heck reaction of 2,3-dihydrofuran with aryl triflate and cyclohexenyl triflate.

Overman and co-workers[257] developed new strategies for the enantioselective formation of quaternary carbons bearing two aryl substituents, as in the synthesis of 3-alkyl-3-aryl-oxindoles using an intramolecular Heck reaction. In several papers,[258] Mikami and co-workers described highly efficient enantioselective syntheses of alkaloids, heterocycles, and carbocyclic spiro compounds via ene-type cyclizations catalyzed by cationic chiral palladium(II) complexes. The first enantioselective intramolecular aminocarbonylation of alkenes promoted by Pd(II)−spiro bis(isoxazoline) catalyst is presented by Sasai and co-workers.[259]

In a related paper,[260] Sasai and co-workers describe the enantioselective synthesis of α-methylene-γ-butyrolactones using a chiral Pd(II)−SPRIX catalyst by an intramolecular cyclization of 2-alkynoates in good yields with up to 92% ee.

A novel enantioselective C−C bond cleavage has been achieved by Uemura and co-workers[261] using palladium catalysts and chiral *N*,*P*-bidentate ligands in the asymmetric arylation, vinylation, and allenylation of *tert*-cyclobutanols. In these reactions, the enantioselective *β*-carbon elimination of Pd(II) alcoholate formed in situ is the key step. Another palladium-catalyzed ring opening is described by Lautens and co-workers,[262] in which an addition of arylboronic acids to heterobicyclic alkenes takes place. An aerobic oxidative kinetic resolution of secondary alcohols was found by Sigman and co-workers[263] using a Pd(II)/(−)-sparteine complex.

20. List of Abbreviations

Ac	acetyl
Ar	aryl
BICP	(2*R*,2′*R*)-bis(diphenylphosphanyl)-(1*R*,1′*R*)-dicyclopentane
BINAP	2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl)
BINAPAs	2-diphenylarsino-2′-diphenylphosphino-1,1′-binaphthyl
BINAPHOS	2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl-1,1′-binaphthalene-2,2′-diyl-phosphite
BINAPO	2-diphenylphosphino-2′-diphenylphosphinyl-1,1′-binaphthalene
BINAs	2,2′-bis(diphenylarsino)-1,1′-binaphthyl
BIPHEP	1,1′- bis(diphenylphosphino)biphenyl
BITIANP	2,2-bis(diphenylphosphino)-3,3′-dibenzo[*b*]-thiophene
Bn	benzyl
BNPPA	(*S*)-1,1′-binaphthyl-2,2′-dihydrogen phosphate
BPPFOAc	1-[1-(acetyloxy)ethyl]-1′,2-bis(diphenylphosphino)ferrocene
BPPFOH	(*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol
COD	cyclooctadiene
Cp	cylopentadienyl
Cy	cyclohexyl
DABN	3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl
dba	(*E*,*E*)-dibenzylideneacetone
DDPPI	1,4,3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-l-iditol
DEAD	diethyl azodicarboxylate
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPOF	oxazolinylferrocenyldiphenylphosphine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenyl phosphoryl azide
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
DUPHOS	1,2-bis(phospholano)benzene
Et	ethyl
*i*Pr	isopropyl
JOSIPHOS	1-[(1*S*)-2-(diphenylphosphanyl)ferrocenyl]-ethyldicyclohexylphosphane
Me	methyl
MOD-DIOP	1,4-bis[bis(3,5-dimethyl-4-methoxyphenyl)-phosphanylmyrthyl]-2,2-dimethyl-1,3-dioxolane
MS	molecular sieves
HMDS	hexamethyldisilazide
*n*Bu	*n*-butyl
*n*Hept	*n*-heptyl
NMP	*N*-methyl-2-pyrrolidone
*n*Pent	*n*-pentyl
Nu	nucleophile
*n*Oct	*n*-octyl
ONf	nonaflate
Ph	phenyl
PMDS	pentamethyldisiloxane
PMP	1,2,2,6,6-pentamethylpiperidine
PPFA	*N*,*N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
Pv	pivaloyl
py	pyridine
SEGPHOS	(4,4′-bi-1,3-benzodioxole)-5,5′-diyl-bis(diphenylphosphine)
SEM	2-(trimethylsilyl)ethyloxymethyl
SPRIX	spiro bis(isoxazoline)
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butoxycarbonyl
Tf	trifluoromethane sulfonyl
TFA	trifluoroacetic acid, trifluoroacetate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMU	tetramethylurea
TPS	*tert*-butyldiphenylsilyl
Tr	trityl

TRAP	(*R*,*R*)-2,2′-bis[(*S*)-1-(diethylphosphanyl)ethyl]-1,1′-biferrocene
Ts	*p*-toluenesulfonyl

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22. References

(1) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999. (c) *Handbook of Palladium-Catalyzed Organic Reactions*; Malleron, J.-L., Fiaud, J.-C., Legros, J.-Y., Eds.; Academic Press: London, 1997. (d) *Palladium Reagents and Catalysts*; Tsuji, J., Ed.; Wiley: Chichester, 1995.

(2) (a) Thematic issue on "Recoverable Catalysts and Reagents" (Gladysz, J. A., Ed.): *Chem. Rev.* **2002**, *102*, 3215. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (c) Sheldon, R. A. *C. R. Acad. Sci., Ser. IIc: Chim.* **2000**, *3*, 541. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(3) a) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 39. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (c) Tietze, L. F.; Lieb, M. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363. (d) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(4) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

(5) Shibasaki, M. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, CT, 1996; p 119.

(6) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

(7) (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Am. Chem. Soc.* **1995**, *117*, 9911. (b) Brookhart, M.; Wagner, M. I.; Balavoine, G. G. A.; Haddou, H. A. *J. Am. Chem. Soc.* **1994**, *116*, 3641. (c) Jiang, Z.; Adams, S. E.; Sen, A. *Macromolecules* **1994**, *27*, 2694. (d) Bronco, S.; Consiglio, G.; Hutter, R.; Batistini, A.; Suter, U. W. *Macromolecules* **1994**, *27*, 4436.

(8) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(9) (a) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (b) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195. (c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (d) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 325. (e) Lübbers, T.; Metz, P. In *Stereoselective Synthesis, Methoden Org. Chem. (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; 1995; Vol. E21, pp 2371 and 5643. (f) Lautens, M. A.; Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, Chapter 24. (g) Williams, J. M. J. *Synlett* **1996**, 705. (h) Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 6291. (i) Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3252. (j) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (k) Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083. (l) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (m) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905. (n) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206 and references therein. (o) Nettekoven, U.; Widhalm, M.; Kalchhauser, H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *J. Org. Chem.* **2001**, *66*, 759. (p) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807. (q) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933. (r) Lee, S.-G.; Lim, C. W.; Song, C. E.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445 and references therein.

(10) (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (b) Constantieux, T.; Brunel, J.-M.; Labande, A.; Buono, G. *Synlett* **1998**, 49. (c) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Org. Chem.* **1999**, *64*, 2994. (d) Breeden, S.; Wills, M. *J. Org. Chem.* **1999**, *64*, 9735. (e) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031. (f) Malone, Y. M.; Guiry, P. J. *J. Organomet. Chem.* **2000**, *603*, 110.

(11) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4544.

(12) (a) Eichelmann, H.; Gais, H.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 643. (b) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

(13) (a) Kawatsura, M.; Uozumi, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron* **2000**, *56*, 2247. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

(14) (a) Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569. (b) Trost, B. M.; Schroder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (c) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (d) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309. (e) Sawamura, M.; Nakayama, Y.; Tang, W.-M.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 9090. (f) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (g) Kuwano, R.; Nishi, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837. (h) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236.

(15) (a) Humphries, A. C.; Pfaltz, A. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 89. (b) Tenaglia, A.; Heumann, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2180. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.

(16) Recent reviews on the Heck reaction: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) de Meijere, A.; Meyer, F. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 3. (c) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 6, p 231. (d) Dounay, M. L.; Overman L. E. *Chem. Rev.* **2003**, *103*, 2945. (e) Beller, M.; Riermeir, T. H.; Stark, G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 208.

(17) Recent reviews on the asymmetric Heck reaction: (a) Shibasaki, M.; Miyazaki, F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002; Vol. 1, Chapter IV, p 1283. (b) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8G. (c) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (d) Shibasaki, M.; Vogl, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 14. (e) Guiry, P. J.; Hennessy, A. J.; Cahill, J. P. *Top. Catal.* **1997**, *4*, 311. (f) Shibasaki, M. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, CT, 1996; Vol. 5, p 119. (g) Sodeoka, M.; Shibasaki, M. *Pure Appl. Chem.* **1998**, *70*, 411. (h) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

(18) Review on the intermolecular asymmetric Heck reaction: (a) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, M.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16. (b) Loiseleur, O.; Hayashi, M.; Schmees, M.; Pfaltz, A. *Synthesis* **1997**, 1338.

(19) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

(20) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

(21) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(22) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(23) (a) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657. (b) Brown, J. M.; Perez-Torrente, J. J.; Alcock, N. W.; Clase, H. J. *Organometallics* **1995**, *14*, 207.

(24) (a) Tietze, L. F.; Schimpf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1089. (b) Tietze, L. F.; O. Burkhardt, O. *Liebigs Ann. Chem.* **1995**, 1153.

(25) (a) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (b) Kojima, A.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3459. (c) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953.

(26) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593.
(27) (a) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965. (b) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371.
(28) (a) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093−4094. (b) Kagechika, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **1993**, *49*, 1773.
(29) (a) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4219. (b) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Synthesis* **1993**, 920.
(30) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737.
(31) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.
(32) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757.
(33) Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303.
(34) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.
(35) Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090.
(36) Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108.
(37) (a) Tietze, L. F.; Raschke, T. *Synlett* **1995**, 597. (b) Tietze, L. F.; Raschke, T. *Liebigs Ann. Chem.* **1996**, 1981.
(38) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolò, F. *Chem. Commun.* **2000**, 583.
(39) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.
(40) Overman, L. E.; Poon, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 518.
(41) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.
(42) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.
(43) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
(44) (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (b) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596.
(45) Grigg, R.; Dorrity, M. J. R.; Malone, J. F.; Mongkolaussavaratana, T.; Norbert, W. D. J. A.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 3075.
(46) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439.
(47) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477.
(48) (a) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 4876. (b) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *Synthesis* **1998**, 581.
(49) Cho, S. Y.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 1773.
(50) Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4322.
(51) Kondo, K.; Sodeoka, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2453.
(52) Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311.
(53) (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147. (b) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595.
(54) Cheng, C.-Y.; Liou, J.-P.; Lee, M.-J. *Tetrahedron Lett.* **1997**, *38*, 4571.
(55) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
(56) (a) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766. (b) Miyazaki, F.; Uotsu, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073. (c) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605. (d) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.
(57) Flubacher, D.; Helmchen, G. *Tetrahedron Lett.* **1999**, *40*, 3867.
(58) Bräse, S. *Synlett* **1999**, 1654.
(59) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421. (c) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485. (d) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yangi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188. (e) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984.
(60) (a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200. (b) Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
(61) (a) Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315. (b) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670.
(62) Tietze, L. F.; Thede, K.; Sannicolò, F. *Chem. Commun.* **1999**, 1811.
(63) Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817.
(64) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Commun.* **2000**, 1483.
(65) Ogasawara, M.; Yoshida, K.; Hayashi, T. *Heterocycles* **2000**, *52*, 195.
(66) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K.-G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40.
(67) (a) Gilbertson, S. R.; Fu, Z.; Xie, D. *Tetrahedron Lett.* **2001**, *42*, 365. (b) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240.
(68) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001** *3*, 161.
(69) Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205.
(70) Kilroy, T. G.; Hennessy, A. J.; Connolly, D. J.; Malone, Y. M.; Farrell, A.; Guiry, P. J. *J. Mol. Catal. A: Chem.* **2003**, *196*, 65.
(71) Bernardinelli, G. H.; Kündig, E. P.; Meier, P.; Pfaltz, A.; Radkowski, K.; Zimmermann, N.; Neuburger-Zehnder, M. *Helv. Chim. Acta* **2001**, *84*, 3233.
(72) Malkov, A. V.; Bella, M.; Stará, I. G.; Kočovský, P. *Tetrahedron Lett.* **2001**, *42*, 3045.
(73) Che, D.; Andersen, N. G.; Lau, S. Y. W.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1919.
(74) Kang, J.; Lee, J. H.; Im, K. S. *J. Mol. Catal. A*: *Chem.* **2003**, *196*, 55.
(75) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.
(76) Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885.
(77) Kurihara, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Pharm. Bull.* **1994**, *42*, 2357.
(78) (a) Hennessy, A. J.; Malone, Y. M.; Guiry, P. J. *Tetrahedron Lett.* **1999**, *40*, 9163. (b) Hennessy, A. J.; Malone, Y.; Guiry, P. J. *Tetrahedron Lett.* **2000**, *41*, 2261.
(79) Hennessy, A. J.; Connolly, D. J.; Malone, Y. M.; Guiry, P. J. *Tetrahedron Lett.* **2000**, *41*, 7757.
(80) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845.
(81) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081.
(82) Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 1227.
(83) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267.
(84) Tietze, L. F.; Thede, K. *Synlett* **2000**, 1470.
(85) Sonesson, C.; Larhed, M.; Nyqvist, C.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 4756.
(86) (a) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129. (b) Priego, J.; Carretero, J. C. *Synlett* **1999**, 1603.
(87) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430.
(88) (a) Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* **2002**, 1611. (b) Bremberg, U.; Lutsenko, S.; Kaiser, N.-F.; Larhed, M.; Hallberg, A.; Moberg, C. *Synthesis* **2000**, 1004.
(89) Brunner, H.; Kramler, K. *Synthesis* **1991**, 1121.
(90) (a) Sakuraba, S.; Awano, K.; Achiwa, K. *Synlett* **1994**, 291. (b) Sakuraba, S.; Okada, T.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 927.
(91) (a) Wu, X.-Y.; Xu, H.-D.; Zhou, Q.-L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 1255. (b) Wu, X.-Y.; Xu, H.-D.; Tang, F.-Y.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2001**, *12*, 2565. (c) Li, X.-G.; Tang, F.-Y.; Xu, H.-D.; Wu, X.-Y.; Zhou, Q.-L. *ARKIVOC* **2003**, *II*, 15.
(92) Namyslo, J. C.; Kaufmann, D. E. *Chem. Ber.* **1997**, *130*, 1327.
(93) Drago, D.; Pregosin, P. S. *Organometallics* **2002**, *21*, 1208.
(94) Ozawa, F.; Kobatake, Y.; Kubo, A.; Hayashi, T. *Chem. Commun.* **1994**, 1323.
(95) Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051.
(96) Namyslo, J. C.; Kaufmann, D. E. *Synlett* **1999**, 804.
(97) (a) Brunel, J. M.; Hirlemann, M.-H.; Heumann, A.; Buono, G. *Chem. Commun.* **2000**, 1869. (b) Brunel, J. M.; Hirlemann, M.-H.; Heumann, A.; Buono, G. *Chem. Commun.* **2002**, 1318.
(98) Diaz, P.; Gendre, F.; Stella, L.; Charpentier, B. *Tetrahedron* **1998**, *54*, 4579.
(99) Hiroi, K.; Kato, F.; Yamagata, A. *Chem. Lett.* **1998**, 397.
(100) (a) Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089. (b) Genêt, J. P.; Grisoni, S.; *Tetrahedron Lett.* **1988**, *29*, 4543. (c) Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 3531.
(101) (a) Achiral reaction: Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387. (b) Ma, S.; Shi, Z.; Wu, S. *Tetrahedron: Asymmetry* **2001**, *12*, 193.
(102) Ma, S.; Shi, Z. *Chem. Commun.* **2002**, 540.
(103) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.
(104) (a) Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312. (b) Achiral reaction: Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482.
(105) Hiroi, K.; Hiratsuka, Y.; Watanabe, K.; Abe, I.; Kato, F.; Hiroi, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1351.
(106) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
(107) Trost, B. M. *Chem. Eur. J.* **1998**, *4*, 2405.

(108) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.
(109) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651.
(110) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211.
(111) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662.
(112) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249.
(113) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704.
(114) (a) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (b) Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* **2001**, *66*, 7676. (c) Lu, X.; Zhang, Q. *Pure Appl. Chem.* **2001**, *73*, 247.
(115) (a) Tkatchenko, I. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1982; Vol. 8, p 101. (b) Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1987; p 232. (c) Hegedus, L. S. *Transition Metals in Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; Chapter 4. (d) Ungvary, F. *Coord. Chem. Rev.* **1998**, *170*, 245. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (f) Agbossu, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485.
(116) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.
(117) (a) Nefkens, S. C. A.; Sperrle, M.; Consiglio, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1719. (b) Sperrle, M.; Consiglio, G. *J. Mol. Catal. A: Chem.* **1999**, *143*, 263.
(118) Takeuchi, S.; Ukaji, Y.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955.
(119) Hayashi, M.; Takezaki, H.; Hashimoto, Y.; Takaoki, K.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 7529.
(120) Sperrle, M.; Consiglio, G. *J. Organomet. Chem.* **1996**, *506*, 177.
(121) (a) Xio, W.-J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 6229. (b) Achiral version: Xio, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4138.
(122) (a) Copéret, C.; Ma, S.; Negishi, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2125. (b) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.
(123) (a) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264. (b) Brunner, M.; Alper, H. *J. Org. Chem.* **1997**, *62*, 7565.
(124) El Ali, B.; Alper, H. *Synlett* **2000**, 161.
(125) Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun.* **1990**, 135.
(126) Yu, W.-Y.; Bensimon, C.; Alper, H. *Chem. Eur. J.* **1997**, *3*, 417.
(127) (a) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708. (b) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905. (c) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1996**, *118*, 2309 [erratum for *J. Am. Chem. Soc.* **1995**, *117*, 10905].
(128) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2307.
(129) Kato, K.; Tanaka, M.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 1511.
(130) Iwata, T.; Miyake, Y.; Nishibayashi, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1548.
(131) Arzoumanian, H.; Buono, G.; Choukrad, M'B.; Petrignani, J. F. *Organometallics* **1988**, *7*, 59.
(132) Gotov, B.; Schmalz, H.-G. *Org. Lett*, **2001**, *3*, 1753.
(133) Suzuki, T.; Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593.
(134) Hayashi, T.; Tang, J.; Kato, K. *Org. Lett.* **1999**, *1*, 1487.
(135) (a) Yuan, J.-C.; Lu, S.-J. *Tetrahedron Lett.* **2001**, *42*, 4069. (b) Yuan, J.-C.; Zhang, Y.-H.; Cheng, M. D.; Lu, S. J. *J. Mol. Catal. A: Chem.* **2001**, *174*, 63. (c) Yuan, J.-C.; Lu, S. J. *Organometallics* **2001**, *20*, 2697. (d) Yuan, J.-C.; Chen, M. D.; Zhang, Y.-H.; Lu, S. J. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 2027.
(136) Reetz, M. T.; Haderlein, G.; Angermund, K. *J. Am. Chem. Soc.* **2000**, *122*, 996.
(137) (a) Nozaki, K.; Hiyama, T. *J. Organomet. Chem.* **1999**, *576*, 248. (b) Consiglio, G. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, Chapter VI.4.2, p 2559.
(138) (a) Barsacchi, M.; Batistini, A.; Consiglio, G.; Suter, U. W. *Macromolecules* **1992**, *25*, 3604. (b) Consiglio, G. *Chimia* **1996**, *50*, 73. (c) Sperrle, M.; Consiglio, G. *J. Am. Chem. Soc.* **1995**, *117*, 12130.
(139) (a) Jiang, Z.; Sen, A. *J. Am. Chem. Soc.* **1995**, *117*, 4455. (b) Sen, A. *Acc. Chem. Res.* **1993**, *26*, 303.
(140) (a) Nozaki, K.; Sato, N.; Tonomura, Y.; Yasutomi, M.; Takaya, H.; Hiyama, T.; Matsubara, T.; Koga, N. *J. Am. Chem. Soc.* **1997**, *119*, 12779. (b) Nozaki, K.; Yasutoni, M.; Nakamoto, K.; Hiyama, T. *Polyhedron* **1998**, *17*, 1159.
(141) Brookhart, M.; Wagner, M. I. *J. Am. Chem. Soc.* **1996**, *118*, 7219.
(142) (a) Aeby, A.; Consiglio, G. *Helv. Chim. Acta* **1998**, *81*, 35. (b) Sperrle, M.; Aeby, A.; Consiglio, G.; Pfaltz, A. *Helv. Chim. Acta* **1996**, *79*, 1387.
(143) (a) Bronco, S.; Consiglio, G.; Di Benedetto, S.; Fehr, M.; Spindler, F.; Togni, A. *Helv. Chim. Acta* **1995**, *78*, 883. (b) Sesto, B.; Bronco, S.; Gindro, E. L.; Consiglio, G. *Macromol. Chem. Phys.* **2001**, *201*, 2059.
(144) Gambs, C.; Chaloupka, S.; Consiglio, G.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2486.
(145) (a) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089. (b) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129 and references therein.
(146) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253.
(147) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157.
(148) Nakano, H.; Okuyama, Y.; Suzuki, Y.; Fujita, R.; Kabuto, C. *Chem. Commun.* **2002**, 1146.
(149) Nakano, H.; Suzuki, Y.; Kabuto, C.; Fujita, R.; Hongo, H. *J. Org. Chem.* **2002**, *67*, 5011.
(150) Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1841.
(151) Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2001**, *12*, 3067.
(152) Benincori, T.; Gladiali, S.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2001**, *66*, 5940.
(153) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160.
(154) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660.
(155) (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, 189, 1−120. (b) Recent review: Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.
(156) (a) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett.* **2002**, *4*, 91. (b) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett.* **2002**, *4*, 95. (c) Mikami, K.; Aikawa, K. *Org. Lett.* **2002**, *4*, 99.
(157) Yamamoto, A.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 375.
(158) (a) Review: Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (c) Seerden, J.-P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441. (d) Gothelf, K. V.; Thomsen, I.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346.
(159) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5947.
(160) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017.
(161) (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (b) Shibata, I.; Toyota, M.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1990**, *55*, 2487. (c) Karikomi, M.; Yamazaki, T.; Toda, T. *Chem. Lett.* **1993**, 1965. (d) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968.
(162) Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700.
(163) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709.
(164) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229.
(165) Larksarp, C.; Sellier, O.; Alper, H. *J. Org. Chem.* **2001**, *66*, 3502.
(166) (a) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126. (b) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938. (c) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954.
(167) (a) Nesper, R.; Pregosin, P. S.; Püntener, K.; Wörle, M. *Helv. Chim. Acta* **1993**, *76*, 2239. (b) Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793.
(168) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648.
(169) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463.
(170) Beletskaya, I. P.; Cheprakov, A. V. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol II, p 2997 (ref 254 in the book is missing).
(171) (a) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, *17*, 4374. (b) Motoyama, Y.; Kawakami, H.; Shimozono; K.; Aoki, K.; Nishiyama, H. *Organometallics* **2002**, *21*, 3408.
(172) (a) Hanzawa, Y.; Tabuchi, N.; Saito, K.; Noguchi, S.; Taguchi, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2395. (b) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 8141. (c) Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron* **2002**, *58*, 7559.
(173) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059.
(174) (a) Review: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Arend, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2873. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
(175) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474.
(176) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.
(177) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548.
(178) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.
(179) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614.
(180) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240.
(181) (a) Negishi, E.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1997; Chapter 1, p 1. (b) Sonogashira, K. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-

VCH: Weinheim, 1997; Chapter 5, p 203. (c) Hayashi, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, Chapter III, Sect. 2.16, p 791. (d) Hayashi. T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 25, p 887.

(182) See also: Shimada, T.; Cho, Y.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396.

(183) Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455.

(184) Kamikawa, T.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 3161.

(185) (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (b) Jedlicka, B.; Kratky, C.; Weissensteiner, W.; Wildhalm, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1329. (c) Hayashi, M.; Kaoki, K. T.; Hashimoto, Y.; Saigo, K. *Enantiomer* **1997**, *2*, 293. (d) Cross, G.; Vriesema, B. K.; Boven, G.; Kellog, R. M.; van Bolhuis, F. *J. Organomet. Chem.* **1989**, *370*, 357.

(186) (a) Hayashi, T.; Yamamoto, A.; Hojo, M.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 495. (b) Uemura, M.; Miyake, R.; Nishimura, H.; Matsumoto, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 213. (c) Hayashi, T.; Yamamoto, A.; Hojo, M.; Kishi, K.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Organomet. Chem.* **1989**, *370*, 129. (d) Hayashi, T.; Hagihara, T.; Katsuro, Y.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363.

(187) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950.

(188) (a) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772. (b) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962.

(189) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723.

(190) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(191) Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymmetry*, **1998**, *9*, 3751.

(192) (a) Åhman, J.; Wolfe, J. P.; Troutman, M. T.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(193) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

(194) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.

(195) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.

(196) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704.

(197) (a) Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442. (b) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954. (c) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

(198) (a) Lautens, M.; Renaud, J. L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J. L. *Org. Lett.* **2000**, *2*, 1971.

(199) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834.

(200) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.

(201) (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089. (b) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217.

(202) Trost, B. M.; Jäkel, C.; Pleitker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438.

(203) (a) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (b) Review: Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 303. (b) Nishiyama, H., Itoh, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 2000; p 111. (c) Hayashi, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 7. (d) Jun, T.; Hayashi, T. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; p 73.

(204) (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 713.

(205) Pioda, G.; Togni, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3903.

(206) Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2335.

(207) (a) Kitayama, K.; Uozumi, Y.; Hayashi, T. *Chem. Commun.* **1995**, 1533. (b) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *Chem. Lett.* **2000**, 1272.

(208) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441.

(209) Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558.

(210) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982.

(211) Gladiali, S.; Pulacchini, S.; Fabbri, D.; Manassero, M.; Sansoni, M. *Tetrahedron: Asymmetry* **1998**, *9*, 391.

(212) Bringmann, G.; Wuzik, A.; Breuning, M.; Henschel, P.; Peters, K.; Peters, E.-M. *Tetrahedron: Asymmetry* **1999**, *10*, 3025.

(213) (a) Ohmura, H.; Matsuhashi, H.; Tanaka, M.; Kuroboshi, M.; Hiyama, T.; Hatanaka, Y.; Goda, K. *J. Organomet. Chem.* **1995**, *499*, 167. (b) Hatanaka, Y.; Goda, K.; Yamashita, F.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 7981. (c) Bäckvall, J.-E. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1997; Chapter 8, p 339. (d) Hiyama, T. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1997; Chapter 10, p 421.

(214) Kitayama, K.; Tsuji, H.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 4169.

(215) Hayashi, T.; Han, J. W.; Takeda, A.; Tang, J.; Nohmi, K.; Mukaide, K.; Tsuji, H.; Uozumi, Y. *Adv. Synth. Catal.* **2001**, *343*, 279.

(216) Han, J. W.; Hayashi, T. *Tetrahedron: Asymmetry* **2002**, *13*, 325.

(217) Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J. W.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 1584.

(218) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1468.

(219) (a) Widenhoefer, R. A.; DeCarli, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3805. (b) Stengone, C. N.; Widenhoefer, R. A. *Tetrahedron Lett.* **1999**, *40*, 1451.

(220) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960.

(221) Perch, N. S.; Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2000**, *65*, 3836.

(222) Pei, T.; Widenhoefer, R. A. *Org. Lett.* **2000**, *2*, 1469.

(223) Pei, T.; Widenhoefer, R. A. *Tetrahedron Lett.* **2000**, *41*, 7597.

(224) Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 7639.

(225) For hydroamination of 1,3-dienes, see: Maddock, S. M.; Finn, M. G. *Organometallics* **2000**, *19*, 2684.

(226) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

(227) (a) Ramachandran, P. V., Ed. *Asymmetric Fluoroorganic Chemistry: Synthesis, Application and Future Directions*; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000. (b) Soloshonok, V. A., Ed. *Enantiocontrolled Synthesis of Fluoro-organic Compounds: Stereochemical Challenges and Biomedical Targets*; Wiley: New York, 1999.

(228) (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979.

(229) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.

(230) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.

(231) (a) Stangl, H.; Jira, R. *Tetrahedron Lett.* **1970**, 3589. (b) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(232) (a) Francis, J. W.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1995**, *99*, 77. (b) Lai, J.-Y.; Wang, F.-S.; Guo, G.-Z.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 6944.

(233) (a) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790. (b) Hamed, O.; Henry, P. M. *Organometallics* **1998**, *17*, 5184. (c) El-Qisairi, A.; Henry, P. M. *J. Organomet. Chem.* **2000**, *603*, 50. (d) El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *J. Organomet. Chem.* **2002**, *656*, 168.

(234) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439.

(235) El-Qisairi, A. K.; Qaseer, H. A.; Henry, P. M. *Tetrahedron Lett.* **2002**, *43*, 4229.

(236) (a) Itami, K.; Palmgren, A.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 6466. (b) Thorarensen, A.; Palmgren, A.; Itami, K.; Bäckvall, J. E. *Tetrahedron Lett.* **1997**, *38*, 8541.

(237) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459.

(238) (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318. (b) Hosokowa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.

(239) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063.

(240) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071.

(241) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620.

(242) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907.

(243) Ito, K.; Ishii, A.; Kuroda, T.; Katsuki, T. *Synlett* **2003**, 643.

(244) (a) Paneghetti, C.; Govagnin, R.; Pinna, F.; Strukul, G. *Organometallics* **1999**, *18*, 5057 and references therein. (b) Bolm, C.; Beckmann, O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 803.

(245) (a) Blaser, H. U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 247. (b) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841. (e) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421. (f) Tietze, L. F.; Zhou, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, *2045*. (g) Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org.*

Chem. **2000**, 2247. (h) Tietze, L. F.; Rackelmann, N. *Angew. Chem., Int. Ed*. **2003**, *42*, 4254.
(246) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett*. **2001**, *3*, 313 and references therein.
(247) Teunissen, H. T.; Elsevier, C. J. *Chem. Commun*. **1998**, 1367.
(248) Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. *Chem. Commun*. **2000**, 1925.
(249) Blaser, H.-U.; Hönig, H.; Studer, M.; Wedemeyer-Exl, C. *J. Mol. Catal. A: Chem*. **1999**, *139*, 253.
(250) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Mura, S., Ed.; Springer: New York, 1999; p 97.
(251) Murakami, M.; Amii, H.; Ito, Y. *Rh Catalyzed Asymmetric Hydrogenolysis of* α*-C*−*C Bond of Cyclobutanone*; Presented at the 69th Annual Meeting of Chemical Society of Japan, March 1995, Kyoto; Abstract II, p 1127.
(252) (a) Nishimura, T.; Matsumara, S.; Maeda, Y.; Uemura, S. *Chem. Commun*. **2002**, 50. (b) For the achiral reaction: Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 11010.
(253) Motoyama, Y.; Nishiyama, H. *Yuki Gosei Kagaku Kyokaishi* **2003**, *61*, 343.
(254) RajanBabu, T. V. *Chem. Rev*. **2003**, *103*, 2845.
(255) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res*. **2003**, *36*, 48.
(256) Tu, T.; Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C. *Chem. Eur. J*. **2003**, *9*, 3073.
(257) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc*. **2003**, *125*, 6261.
(258) (a) Hatano, M.; Mikami, K. *Org. Biomol. Chem*. **2003**, *1*, 3871. (b) Hatano, M.; Mikami, K. *J. Am. Chem. Soc*. **2003**, *125*, 4704. (c) Hatano, Manabu; Mikai, K. *J. Mol. Catal. A: Chem*. **2003**, *196*, 165. (d) Hatano, M.; Yamanaka, M.; Mikami, K. *Eur. J. Org. Chem*. **2003**, 2552.
(259) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett*. **2003**, *5*, 1809.
(260) Muthiah, C.; Arai, M. A.; Shinohara, T.; Arai, T.; Takizawa, S.; Sasai, H. *Tetrahedron Lett*. **2003**, *44*, 5201.
(261) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **2003**, *125*, 8862.
(262) Lautens, M.; Dockendorff, C. *Org. Lett*. **2003**, *5*, 3695.
(263) Mandal, S. K.; Jensen, D. R., Pugsley, J. S.; Sigman, M. S. *J. Org. Chem*. **2003**, *68*, 4600.

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