THE NEGISHI COUPLING: AN UPDATE

Aldrichimica Acta

VOL. 38, NO. 3 • 2005

Palladium-Catalyzed Alkenylation by the Negishi Coupling

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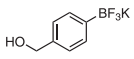
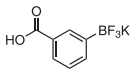
TRIFLUOROBORATES

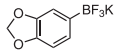
Potassium 4-(hydroxymethyl)phenyltrifluoroborate

659762  1 g, 5 g

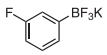
Potassium 3-carboxyphenyltrifluoroborate

659789  1 g, 5 g

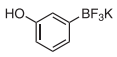
Potassium 3,4-(methylenedioxy)phenyltrifluoroborate

659754  1 g, 5 g

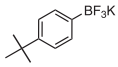
Potassium 3-fluorophenyltrifluoroborate

659770  1 g, 5 g

Potassium 3-hydroxyphenyltrifluoroborate

659746  1 g, 5 g

Potassium 4-*tert*-butylphenyltrifluoroborate, 95%

654728  1 g, 10 g

Potassium 2-methoxyphenyltrifluoroborate

654930  1 g, 5 g

Potassium vinyltrifluoroborate, 95%

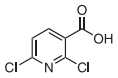
655228  1 g, 5 g

Trifluoroborates are air-stable alternatives to boronic acids in the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[1–3] They are more robust, easier to handle, and less prone to protodeboronation.[1] They display a remarkably uniform behavior.[2]

(1) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (2) Molander, G. A. et al. *J. Org. Chem.* **2003**, *68*, 5534. (3) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49.

BUILDING BLOCKS

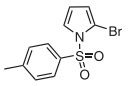
2,6-Dichloronicotinic acid, 97%

658219  1 g, 5 g

This pharmaceutical research[1,2] key building block is now available in 97% purity. See **479586** for a technical grade (90%) of this material.

(1) Kelly, T. P. et al. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 451. (2) Laeckmann, D. et al. *Bioorg. Med. Chem.* **2002**, *10*, 1793.

2-Bromo-1-(*p*-toluenesulfonyl)pyrrole, 90%

650900  1 g, 5 g

This product is a stable and easily handled alternative for the labile bromopyrrole, and is an excellent substrate for the Suzuki coupling reaction. The tosyl group is readily cleaved under basic conditions to generate the 2-arylpyrrole coupling product.

Knight, L. W. et al. *Synlett* **2003**, 1993.

N-Boc-piperidine, 98%

655872  5 g, 25 g

A wide variety of substituted piperidines can be synthesized from this Boc-protected building block. Lithiation with BuLi leads to substitution at the 2 position with aryl, vinyl, and alkynyl halides.[1] Its use in the stereoselective synthesis of D-*threo*-methylphenidate (Ritalin®) and similar substrates has been reported.[2,3]

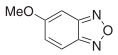
(1) Dieter, R. K.; Li, S. J. *J. Org. Chem.* **1997**, *62*, 7726. (2) Axten, J. M. et al. *J. Am. Chem. Soc.* **1999**, *121*, 6511. (3) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

BENZOFURAZANS

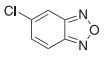
Benzofurazan, 97%

650137  1 g, 10 g

5-Methoxybenzofurazan, 97%

656925  1 g, 5 g

5-Chlorobenzofurazan

659118  1 g, 5 g

Benzofurazans have been utilized as effective fluorescence probe motifs[1] and as medicinal building blocks in the synthesis of antileukemic agents.[2,3]

(1) Uchiyama, S. et al. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2525. (2) Ghosh, P. B.; Whitehouse, M. W. *J. Med. Chem.* **1968**, *11*, 305. (3) Ghosh, P. B.; Whitehouse, M. W. *J. Med. Chem.* **1969**, *12*, 505.

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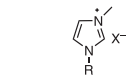
(1) Seddon, K. R.; Stark, A. *Green Chem.* **2002**, *4*, 119. (2) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun.* **1999**, 25. (3) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH, 2003; p 26. (4) Stark, A.; Ajam, M.; Green, M.; Raubenheimer, H. G.; Ranwell, A.; Ondruschka, B. *Adv. Synth. Catal.*, submitted for publication, 2005.



R = Bu, Et; X = Cl, PF_6, BF_4

04129	**1-Butyl-3-methylimidazolium chloride**, puriss., dry, ≥99.0% (AT)	5 g 25 g
55509	**1-Butyl-3-methylimidazolium chloride**, dry, ≥99.0% (AT)	5 g 25 g
18122	**1-Butyl-3-methylimidazolium hexafluorophosphate**, for catalysis, ≥98.5% (T)	5 g 50 g
39931	**1-Butyl-3-methylimidazolium tetrafluoroborate**, for catalysis, ≥98.5% (T)	5 g 50 g
39736	**1-Ethyl-3-methylimidazolium tetrafluoroborate**, for catalysis, ≥98.5% (T)	5 mL 50 mL

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington.

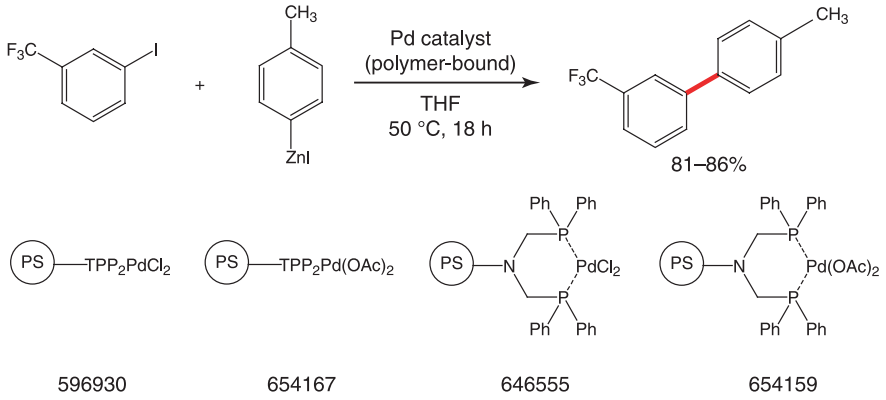
Valdemosa, Majorca: Thistles and Herbage on a Hillside (oil on canvas, 55.8 × 71.1 cm) was painted by the artist John Singer Sargent in 1908. Sargent was born in 1856 in Florence, Italy, to expatriate American parents. His first artistic training was in Rome, but he later attended the Accademia delle Belle Arti in Florence, and studied drawing at the École des Beaux-Arts and painting in the studio of the portrait painter Charles Carolus-Duran in Paris. In 1877, he began to exhibit in the Salons, the French government sanctioned art exhibitions. Sargent copied works by Diego Velázquez on a trip to Spain in 1879 and by Frans Hals in Belgium and Holland in 1880, an experience that had a great impact on his artistic development.

By the end of the nineteenth century, Sargent had become the most sought-after portrait painter of his time, but he always felt constrained by the limitations of portrait painting. By the early twentieth century, his success finally allowed him to free himself almost completely from the painting of formal portraits. He made annual trips to Spain, Italy, Austria, and Switzerland, and it was on a trip to the Balearic island of Majorca that he painted this small picture. He had no interest in what he called "enormous views and huge skies", and chose to concentrate on a small patch of vegetation growing in the earth of a hillside. This painting is not strictly a realistic image, but one which, with its strong formal contrasts, bright colors, and seemingly spontaneous execution, achieves an extraordinary intensity of expression. Confronted with such an immediate response to nature that seems almost spiritual in its intensity, it is easy to understand Sargent's disdain for the artificiality of the academic portrait painting that had dominated his career for most of his life.

This painting was acquired by the National Gallery of Art, Washington, DC, through the Avalon Fund and by Gift of Virginia Bailey Brown.

The Negishi Coupling Catalyzed by Palladium on Polymer Supports

Supported palladium catalysts are widely used in the Suzuki, Heck, and Sonogashira cross-coupling reactions. However, no examples of their use in the Negishi coupling have been reported in the literature. There are several advantages to using supported catalysts in organic synthesis. These include reagent stability, suitability for automation, ease of workup, recyclability, and lower Pd contamination in the final product. Herein, we describe the application of four commercially available polymer-supported palladium reagents as catalysts in the Negishi coupling.



Typical Experimental Procedure

The palladium catalyst (0.01 mmol Pd) is charged into the reaction vessel. 3-Iodobenzotrifluoride (144 µL, 1 mmol) is then introduced, followed by addition of a THF solution of 4-methylphenylzinc iodide (0.5 M, 3 mL, 1.5 mmol). The resulting mixture is stirred at 50 °C for 18 h, cooled, and then filtered. The resin is washed with THF (2 × 3 mL), the THF filtrates combined and evaporated. The evaporation residue is dissolved in a minimum amount of THF and filtered through a silica gel pad to remove any residual zinc compounds. The pad is rinsed with ether, and the combined ether filtrates evaporated. The crude product thus obtained is purified by flash chromatography on silica gel (column size 1.5 × 2.5 cm) using hexane as eluent. The purified product, 4-methyl-3′-trifluoromethylbiphenyl, is isolated as a colorless oil. (See the table below for yields.)

Cat. No.	Catalyst Name	Product Yield	Byproduct Yield[a]
596930-1G **596930-5G**	Dichlorobis(triphenylphosphine)palladium(II), polymer-bound	83%	4%
654167-5G **654167-25G**	Diacetoxybis(triphenylphosphine)palladium(II), polymer-bound	84%	5%
646555-1G **646555-5G**	Bis[(diphenylphosphanyl)methyl]aminepalladium(II) dichloride, polymer-bound	86%	4%
654159-1G **654159-5G**	Bis[(diphenylphosphanyl)methyl]aminepalladium(II) diacetate, polymer-bound	81%	5%

[a] 4,4′-Dimethylbiphenyl.

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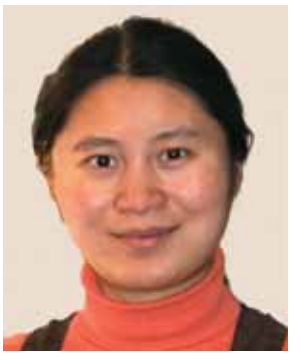
Palladium-Catalyzed Alkenylation by the Negishi Coupling


Professor Ei-ichi Negishi


Ms. Qian Hu

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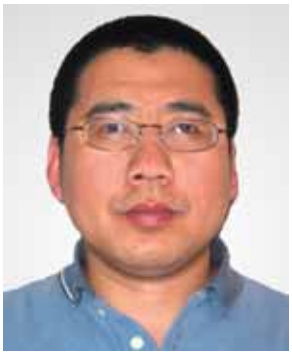
Mr. Zhihong Huang


Dr. Mingxing Qian


Mr. Guangwei Wang

Outline

1. Introduction

The palladium-catalyzed cross-coupling of an organometal (R^1M) with an organic electrophile (R^2X) has emerged over the past thirty years as one of the most general and selective methods for carbon–carbon-bond formation (**eq 1**). Currently, it appears to be generally superior to related methods involving the use of Ni, Cu, or Fe catalysts in its scope and stereo-, regio-, and chemoselectivities.[1] The R^1 group of R^1M can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, cyano, or enoxy; while the R^2 group of R^2X can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, or acyl. Use of other related carbon groups as R^1 and/or R^2 is not only conceivable, but also known in the literature. Even if only those nine types of organometals (R^1M) and eight types of organic electrophiles (R^2X) mentioned above are considered, their binary combinations lead to 72 different types of cross-coupling reactions, and most of these reactions have indeed been developed. Until recently, the use of alkyl electrophiles lacking proximal π bonds had been considered to be categorically very difficult, and the task of Pd-catalyzed alkylation had been achieved by using alkylmetals. The latter is still of much broader synthetic applicability. However, some recent developments suggest that this generalization may have to be significantly modified in the future, as discussed in Section 2.6. Another group of categorically difficult Pd-catalyzed cross-coupling reactions are those involving cross-coupling between allyl, benzyl, and/or propargyl groups.[1a] In addition, a more promising, direct, and selective α alkenylation and α alkynylation of metal enolates[1a,2–4] need to be further developed.

The Pd-catalyzed cross-coupling can be performed with organometals containing any of ten or more different metals including Zn, Al, or Zr (Negishi coupling),[1] B (Suzuki coupling),[1,5,6] Sn (Stille coupling),[1,7] as well as Li,[8] Mg,[9,10] In,[11] Si,[1,12] Cu,[13] and Mn.[14] This review will briefly discuss the Pd-catalyzed alkenylation involving Zn-, Al-, or Zr-containing organometals and leading to the direct formation of a carbon–carbon single bond to alkenyl groups. Its application to the synthesis of alkenes of biological, medicinal, and materials science interest will also be briefly discussed. To indicate various types of cross-coupling, compound adjectives, such as alkenyl–aryl and aryl–alkenyl, are used. In these words, the first and second terms indicate the R^1 and R^2 groups of R^1M and R^2X, respectively. Recent advances in the development of (i) hydrometallation–cross-coupling and carbometallation–cross-coupling tandem processes, and (ii) the selective disubstitution of 1,1- and 1,2-dihaloalkenes will be emphasized. The Pd-catalyzed alkenylation via cross-coupling may be classified into 16 types. Most of these types and results that had been reported prior to 1998 have been comprehensively reviewed elsewhere.[1a] It is worth mentioning, however, that two recent reviews of the Pd-catalyzed alkynylation[1,15] contain many new examples of the Pd-catalyzed alkynyl–alkenyl coupling.

$$R^1M + R^2X \xrightarrow{PdL_n(cat.)} R^1{-}R^2 + MX \qquad \textbf{eq 1}$$

2. The Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals

2.1. Early Findings

Between 1976 and 1978, Negishi's group published close to ten seminal papers on the Pd- or Ni-catalyzed cross-coupling,[16–24] disclosing, for the first time, the following findings pertinent to this review.

i. The Pd- or Ni-catalyzed reaction of alkenylalanes with aryl halides represents the first set of examples of the Pd- or Ni-catalyzed organoalane cross-coupling, and of the Pd- or Ni-catalyzed hydrometallation–cross-coupling tandem reaction.[16]
ii. The alkenyl–alkenyl couplings of *cis*- or *trans*-1-iodo-1-hexene with *trans*-1-(diisobutylalumino)-1-hexene represent the earliest examples of the Pd- or Ni-catalyzed "pair-selective" and stereoselective synthesis of conjugated dienes.[17]
iii. These reactions also demonstrated, for the first time, some distinct advantages of Pd over Ni, e.g., superior stereospecificity: ≥98% (Pd) vs ≥90% (Ni).[17]
iv. The reaction of (*E*)-3-bromo-2-methylacrylic ester provided the first example of generally favorable Pd-catalyzed conjugate substitution.[17,18,22–25]
v. The Pd-catalyzed reaction of alkynylzinc chlorides with alkenyl halides[18]—along with the related alkynyl–aryl,[19] aryl–aryl,[20] and benzyl–aryl[20] coupling reactions—not only provided some of the earliest examples of the Pd-catalyzed cross-coupling of organozincs, but also indicated the superior reactivity of organozincs under the Pd-catalyzed cross-coupling conditions relative to the ten or so other types of organometals mentioned earlier.
vi. Following the discovery of the Ni-catalyzed cross-coupling reaction of alkenylzirconiums with aryl halides in 1977,[21] the Pd-catalyzed alkenyl–alkenyl coupling of alkenylzirconium derivatives with alkenyl halides was reported in 1978.[22]
vii. The first examples of the Pd-catalyzed carboalumination–cross-coupling tandem reaction were also reported in 1978.[23] The use of Zn salts, such as $ZnCl_2$ or $ZnBr_2$, as additives or cocatalysts in the coupling step of this tandem reaction was shown to be highly desirable or even essential to observing satisfactory results. This study demonstrated, for the first time, the concept of double metal catalysis and the favorable effects of additives on the Pd- or Ni-catalyzed cross-coupling.[23]
viii. The findings reported in references 16–23 established that the Pd- or Ni-catalyzed cross-coupling can be achieved with organometals containing various metal countercations other than Mg, which had previously been used almost exclusively. A systematic screening of metal countercations was conducted for the first time for the Pd-catalyzed reaction of alkynylmetals with *o*-tolyl iodide.[24–26] This study indicated that, in addition to alkynylzincs, organometals containing B and Sn were superior reagents, and these were subsequently developed as the Suzuki[1,5,6] and Stille[1,7] coupling reactions, respectively. The reaction of *n*-PentC≡CB(*n*-Bu)$_3$Li with *o*-tolyl iodide, producing the desired *n*-PentC≡C(*o*-Tol) in

92% yield, was the first example of the Pd-catalyzed cross-coupling of organoboron compounds. Further details of the early developments of the Negishi coupling and related cross-coupling reactions are discussed in the pertinent reviews.[25,26]

2.2. Summary of Current Status

2.2.1. Metal Countercations

The Pd-catalyzed cross-coupling has proved to be of wide scope with respect to metal countercations.[1] In many less demanding cases, all or most of the ten or more metals that have been used as countercations may work satisfactorily. In other more demanding cases, however, critical differences among them have been observed. It is therefore desirable to be familiar with the pros and cons of the various available countercations. In view of the multimechanistic and multifaceted nature of the Pd-catalyzed cross-coupling, however, it is not practical to compare and rank them on one scale. From a practical viewpoint, synthetic chemists are generally seeking those methods and reactions that satisfy some or most, if not all, of the following criteria: (i) predictably general applicability, especially with respect to the R^1 and R^2 groups to be coupled, (ii) high product yield, (iii) high regio-, stereo-, and chemoselectivities minimizing the need for separation and purification, (iv) high efficiency including step-economy as well as operational simplicity and convenience, (v) low costs of reagents, catalysts, other materials, and of other aspects of operation, and (vi) high level of safety especially with regards to toxicity as well as explosion and fire hazards.

A priori, organometals containing highly electropositive metals, such as Li and Mg, which are normally considered to be "highly nucleophilic", would be desirable from a reactivity point of view. Conversely, organometals containing highly electronegative metalloids, such as B and Si, might be expected to be of limited reactivity. Under conditions that are stoichiometric in Pd, highly electropositive metals, such as Li and Mg, are at least as reactive as Zn.[27] Under Pd-catalyzed conditions, however, the reactivity order of Zn > Mg >> Li has been observed more often than not.[1,24,27,28] This unexpected order of reactivity has been tentatively interpreted in terms of catalyst poisoning by highly nucleophilic organometals containing Li and Mg. On the other hand, there have also been indications that Grignard reagents display a significantly higher catalytic reactivity than the corresponding organozincs in some cases, such as those involving organic chlorides.[29] Therefore, in cases where Grignard reagents and organolithiums are generated first, they should also be tested in the cross-coupling reaction before converting them into other organometals.

At the end of the nucleophilicity scale lie highly electronegative metals and metalloids, such as B and Si. Organoboranes, as opposed to borates, and organosilanes are as such of very low reactivities at best. In fact, silyl groups are often used as protecting groups. As noted in the first successful Pd-catalyzed organoboron cross-coupling[24–26] vis-à-vis earlier failures with alkenylboranes,[16,17] the reactivity of organoboranes can be substantially increased through ate complexation.[1,5,6] Similar activations of organosilanes with fluorides have also made organosilanes useful in the Pd-catalyzed cross-coupling.[12] Generally speaking, however, it has become increasingly clear that Zn displays the highest reactivity under the Pd-catalyzed conditions, and that its catalytic reactivity is followed by those of several metals of intermediate electronegativity including Al,[16,17,25] In,[11] Sn,[30–32] Zr,[33] and Cu[34] (**Scheme 1**).[1a] Thus, one can expect that high reactivity with respect to the desired cross-coupling—relative to other undesired processes including regio- and stereoisomerizations and catalyst poisoning—should lead to high product yields, a wider scope of cross-coupling, higher selectivities, higher catalyst turnover numbers, and lower cost of operation.

The selection of metal countercations, of course, involves some other factors, such as chemoselectivity, operational convenience including compatibility with water and air, economy, safety, and others. Some of these factors must undoubtedly be responsible for the current widespread use of B and Sn. For toxicity related reasons, however, the use of Sn might be projected to be increasingly limited. On the other hand, it appears that Si might be used more extensively in the future. Along a more scientific line, the facile and convenient preparation of stereo- and regio-defined alkenylmetals and the corresponding halides or related electrophiles is one of the most critical factors in selecting countercations for the Pd-catalyzed alkenylation. Several metals and metalloids such as B, Al, In, Zr, Cu, Si, Sn, and Zn have been used for forming the first-generation alkenylmetals directly from alkynes, rendering these metals attractive countercations in Pd-catalyzed alkenylations.[5,6,34–47] On the other hand, alkenylmetals containing Li and Mg have been prepared mostly from alkenyl halides rather than alkynes. In many cases, the methods of converting alkynes to alkenylmetals are also applicable to the preparation of alkylmetals from alkenes.[48–50] Various types of hydrometallation, carbometallation, and heterometallation including metallometallation have been employed for the Pd-catalyzed alkenylation often in conjunction with the use of Zn or In salts as cocatalysts.

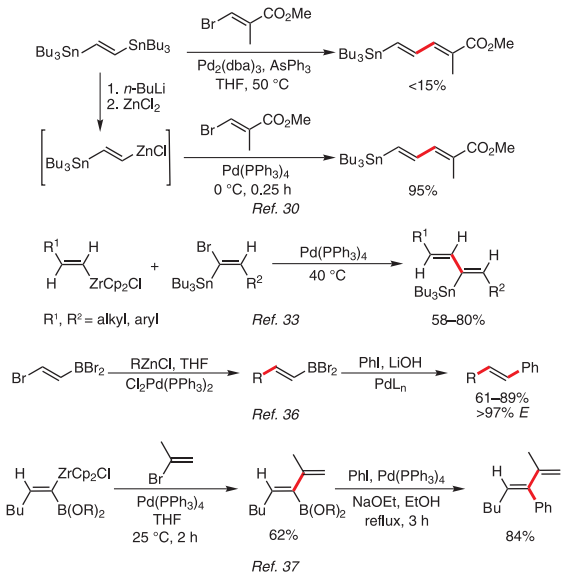
2.2.2. Leaving Groups

Other parameters influencing the Pd-catalyzed alkenylation reaction include the nature of the leaving group (X) in the electrophilic partner (R^2X), the Pd catalyst, cocatalyst or other additive, and solvent. In cases where R^2X represents alkenyl electrophiles, the X group is usually I, Br, Cl, or some oxygen-containing group, such as OTf and $OPO(OR)_2$. For a given R^2 group, the generally observed order of reactivity of halogens is I > Br > Cl. Unfortunately, the generally least expensive, and hence most desirable, Cl-containing electrophile is the least reactive. Therefore, a reasonable course of action might be to choose first the most reactive I- or Br-containing electrophile and see if the desired cross-coupling can be satisfactorily achieved. If the coupling reaction is thus achievable, one may then attempt to use the less expensive Cl or other leaving groups. In this context, a recent report of the reactions of aryl and alkenyl chlorides with aryl- and alkynylzinc chlorides in THF–NMP at 100 °C in the presence of 2 mol % of $Pd[(t\text{-}Bu)_3P]_2$ is noteworthy.[51b]

2.2.3. Pd Catalysts, Cocatalysts or Other Additives, and Solvents

Three other chemical parameters are available for optimizing the reaction conditions: (i) phosphines and other ligands in the Pd catalysts, (ii) cocatalysts and other additives, and (iii) the solvents used. In recent years, some significant advances have been made in the first two categories, especially in ligands. These topics have very recently been discussed in some detail.[1b] Ligands, additives, and solvents specifically utilized in the Pd-catalyzed alkenylation with Zn, Al, and Zr organometals are presented in **Figure 1**.[51–60]

In summary, the selection of an optimal set of parameters for a given Pd-catalyzed cross-coupling is becoming increasingly more involved and at times confusing. Until recently, the combination indicated as *Procedure I (Conventional Standard Conditions)* and employing PPh_3 as the ligand, had been most widely utilized (**Figure 2**). In many less demanding cases, it has worked satisfactorily, and it should still be one of the first-round options.



Scheme 1. The Higher Reactivities Displayed by Zn and Zr Relative to Other Metals in the Pd-Catalyzed Alkenylation.

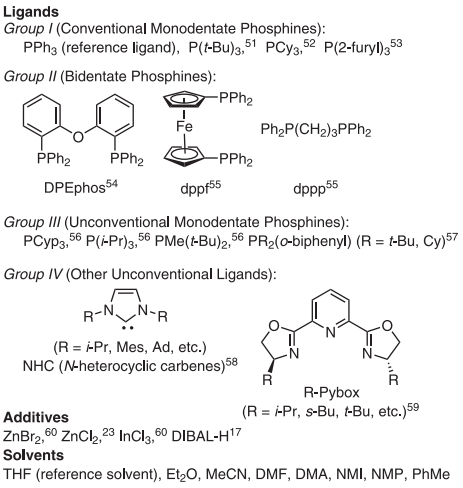


Figure 1. Ligands, Additives, and Solvents Commonly Used in the Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals.

Procedure I (Conventional Standard Conditions):
Catalyst: 1–5 mol % of $Pd(PPh_3)_4$, or several variants of $Pd(PPh_3)_2L_n$ including $Cl_2Pd(PPh_3)_2$ with or without DIBAL-H; $Pd_2(dba)_3$ or $Pd(dba)_2$; $Cl_2Pd(MeCN)_2$; and Li_2PdCl_4 in the presence of PPh_3

Additive: $ZnBr_2$ or $ZnCl_2$, as needed
Solvent: THF and/or DMF

Procedure II (Modern Standard Conditions):
Catalyst: Cl_2Pd(DPEphos), Cl_2Pd(dppf), or Cl_2Pd(dppp)

Catalyst Loading: Initial screening at 1–5 mol % then consider $\leq 10^{-1}$–10^{-3} mol %

Additive: $ZnBr_2$, $ZnCl_2$, or $InCl_3$, as needed
Solvent: THF and/or DMF

Figure 2. Conventional and Modern Standard Conditions for the Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals.

On the other hand, it has become increasingly clear in recent years that some bidentate ligands, such as DPEphos[54] and dppf,[55] are very frequently superior to simple monodentate phosphines. In less demanding cases, their differences may not be readily noticeable or hardly significant, but in other more demanding cases, these differences become significant. *Procedure II (Modern Standard Conditions)*, employing bidentate ligands, should be considered as needed. Yet other procedures may be considered for solving even more difficult problems.

Even in cases where the differences among two or more procedures seem very minor at high catalyst loadings (1–5 mol %), they usually become more noticeable and significant at lower catalyst loadings. The catalyst loading level or catalyst turnover number (TON) is a potentially very significant issue in the practical application of the Pd-catalyzed cross-coupling. For example, even if a Pd catalyst costs $10,000/mol, it would effectively cost a mere $1–10/mol at a TON level of 10^3–10^4. Since the overall cost of operation also depends on the costs of other reagents, the practical value of attaining extremely high TONs (>10^6) may be questioned. Nevertheless, the currently prevalent level of TON $\leq 10^2$ should be elevated to 10^3–10^5 in most cases. Recent studies indicate that the use of some chelating ligands, such as DPEphos and dppf, in conjunction with organometals containing Zn, B, and In, as well as Al–Zn and Zr–Zn combinations, can readily achieve TONs > 10^4.[61]

2.3. Alkenyl–Aryl, Aryl–Alkenyl, and Alkenyl–Alkenyl Coupling Reactions

2.3.1. Alkenyl–Aryl and Aryl–Alkenyl Couplings

Both of these reactions produce aryl–substituted alkenes or styrene derivatives. Both protocols involving the Negishi coupling are generally satisfactory, but the following considerations might be important in choosing one over the other: (i) In cases where the required alkenyl reagents are readily accessible via hydrometallation or carbometallation, first consideration should be given to generating the alkenylmetals in situ and carrying out the alkenyl–aryl cross-coupling in the same pot. (ii) On the other hand, many readily available alkenyl electrophiles, such as vinyl bromide, vinylidene chloride and bromide, and (*E*)-3-bromo-2-methylacrylic acid derivatives, favor the aryl–alkenyl coupling protocol. (iii) In some cases, alkenyl electrophiles are most readily accessible from the corresponding carbonyl compounds in the forms of alkenyl triflates or phosphates. In these cases, the aryl–alkenyl coupling protocol would be favored.

Since Al, Zr, and Zn offer a wide range of hydrometallation and carbometallation reactions, and since Zn along with Al–Zn and Zr–Zn combinations are among the most favorable metals in the Pd-catalyzed cross-coupling, both alkenyl–aryl and aryl–alkenyl Negishi cross-coupling reactions rank among the most satisfactory methods for forming the required C–C bonds. Although the number of applications to the synthesis of natural products is still rather limited, the examples reported thus far point to the potential utility and versatility of these reactions (**Scheme 2**).[62–64] A recent application of the Pd-catalyzed reaction of an alkenylzirconium derivative with a bromoxazole to the synthesis of (–)-diazonamide A is especially noteworthy.[64] Other notable examples include the synthesis of alkenyl-substituted nucleosides[65] and a phorboxazole A model.[66]

2.3.2. Alkenyl–Alkenyl Coupling

Mainly during the past decade, the Pd-catalyzed alkenyl–alkenyl coupling involving Al and Zr has been extensively applied to the synthesis of conjugated dienes and oligoenes (**Table 1**).[67–88] In many of these reactions, $ZnBr_2$ or $ZnCl_2$ was utilized as a promoter or cocatalyst. In some cases where the Al–Zn or Zr–

Zn combination proved to be less than satisfactory, the use of preformed alkenylzincs derived from the corresponding Li or Mg precursors was demonstrated to be generally superior to them. In some cases, however, a useful synergism was observed between Al or Zr and In, which rendered $InCl_3$ superior to $ZnBr_2$ or $ZnCl_2$ as a cocatalyst.[60] Overall, the Pd-catalyzed alkenyl–alkenyl coupling involving Al, Zr, and Zn represents one of the most generally applicable and satisfactory protocols for the synthesis of conjugated dienes and oligoenes. Nevertheless, it should not be overlooked that several other metals and metalloids including Mg, B, Sn, Si, and Cu have also been employed satisfactorily in many cases.[1,5,6,7,9–13]

2.4. Alkynyl–Alkenyl and Alkenyl–Alkynyl Coupling Reactions

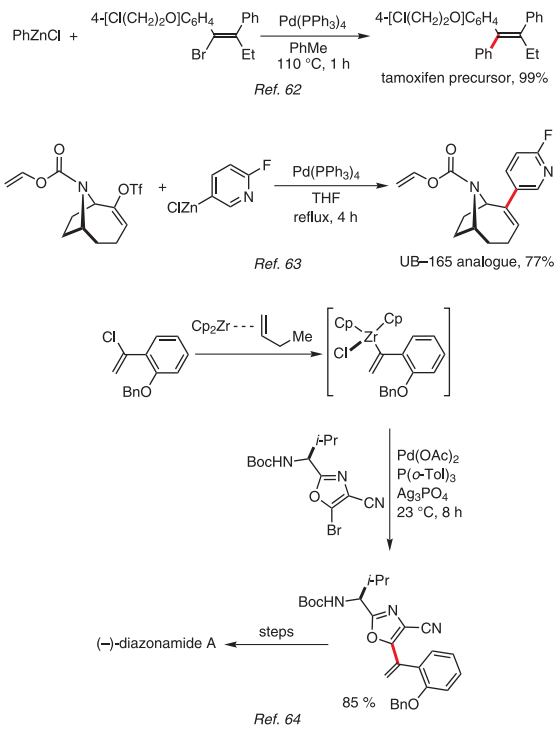
Although the Pd-catalyzed reaction of alkenylmetals containing Al or Zr with 1-iodo-1-hexyne in the presence of $ZnCl_2$ was reported as early as 1978,[23] the alkenyl–alkynyl coupling protocol has not been widely used for the synthesis of conjugated enynes. A notable exception is the synthesis of enediynes by the reaction of (*Z*)-1,2-bis(trimethylstannyl)ethylene with α,ω-diiododiynes.[15] It is generally more convenient to use the alkynyl–alkenyl coupling protocol for the synthesis of conjugated enynes. This reaction utilizes alkynylzincs and provides one of the most satisfactory, generally applicable, and convenient routes to conjugated enynes (**Table 2**).[80,85,87,89–94] In many less demanding cases, the Sonogashira coupling[1a] has probably been most widely used. However, it has recently been shown that its scope is significantly more limited than the alkynylzinc protocol. Thus, for example, it has often been problematic to use alkynes containing electron-withdrawing groups, such as an ester, in the Sonogashira coupling.[15] Direct synthesis of terminal alkynes without protection–deprotection by this reaction has not been practical either. As discussed earlier, it is also possible to use several other classes of alkynylmetals and metalloids containing Mg, B, Al, In, Si, Sn, and others. In cases where alkynylmetals containing Mg are satisfactory, their use should be considered before converting them into other alkynylmetals. Since alkynylmetals containing B, Al, In, Si, and Sn are prepared mainly from alkynylmetals containing Mg, Li, or some other alkali metal, and since they are generally less reactive than alkynylzincs, their use in place of Mg or Zn should be well justified.[1a,15,95]

2.5. Benzylation, Allylation, and Propargylation of Alkenylmetals and Alkenyl Electrophiles

In this section, six types of cross-coupling reactions are discussed. These lead to three types of products: allylarenes (or benzylalkenes), 1,4-dienes, and 1,4-enynes. Relevant findings reported prior to 1998 have been comprehensively reviewed.[1a]

2.5.1. Alkenyl–Benzyl and Benzyl–Alkenyl Coupling Reactions for the Synthesis of Allylarenes

Benzylation by the Pd-catalyzed cross-coupling is a generally favorable process that can be achieved satisfactorily via either alkenyl–benzyl or benzyl–alkenyl coupling. If alkenylmetals are more readily accessible than the corresponding halides, the alkenyl–benzyl coupling may be considered first. If, on the other hand, alkenyl electrophiles are more readily available than the corresponding alkenylmetals, the benzyl–alkenyl coupling should be considered first. It is also important to note that benzylzincs can usually be more cleanly and readily prepared than the corresponding Li- or Mg-containing benzylmetals by direct metallation of benzyl bromides or chlorides with Zn metal with minimum complications arising from homocoupling and other



Scheme 2. Synthesis of Natural Products and Related Compounds via the Negishi Alkenyl–Aryl or Aryl–Alkenyl Coupling.

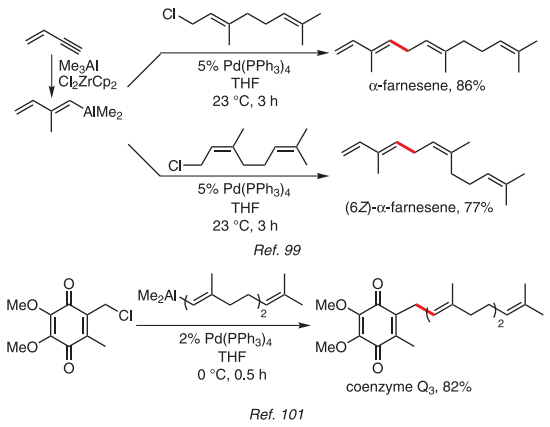
Table 1. The Pd-Catalyzed Alkenyl–Alkenyl Coupling with Al, Zr, and Zn Organometals in Natural Product Synthesis

Year	Natural Product or Related Compound	Major Author	Ref.
1987	Piperovatine	Crombie, L.	67
1991	Methyl dimorphecolate	Duffault, J. M.	68
1991	Vitamin A	Negishi, E.	69
1995	Papulacandin D	Barrett, A. G. M.	70
1996	Discodermolides	Schreiber, S. L.	71
1996	Zaragozic acid C	Paterson, I.	72
1996	Nakienone B	Negishi, E.	73a
1997	Nakienone A	Negishi, E.	73b
1997	Gadain and Savinin	Rossi, R.	74
1998	Okinonellin B	Romo, D.	75
1998	(±)-Carbacyclin	Negishi, E.	76
1999	Lissoclinolide	Negishi, E.	77
1999	Reveromycin B	Theodorakis, E. A.	78
2000	Pitiamide A	Wipf, P.	79
2000	Xerulin	Negishi, E.	80
2001	β- and γ-Carotenes	Negishi, E.	81
2001	Eunicenone A	Corey, E. J.	82
2001	FR901464 (antitumor antibiotic)	Jacobsen, E. N.	83
2002	Motuporin	Panek, J. S.	84
2004	*cis*- and *trans*-Bupleurynol	Organ, M. G.	85
2004	(–)-Callystatin A	Panek, J. S.	86
2004	6,7-Dehydrostipiamide	Negishi, E.	87
2004	Xerulinic acid	Brückner, R.	88

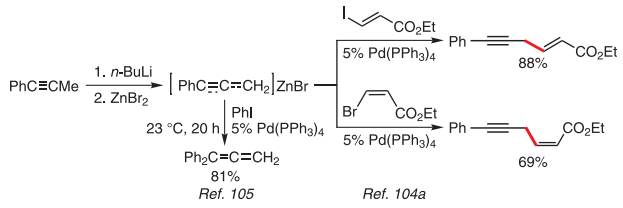
Table 2. The Pd-Catalyzed Coupling between Alkynylmetals Containing Zn or Mg and Alkenyl Electrophiles in Natural Product Synthesis

Year	Natural Product or Related Compound	Major Author	Ref.
1982	Octa-2,3-dien-5,7-diyn-1-ol[a]	Vermeer, P.	89
1988	Marasin	Boersma, J.	90
1997	Freelingyne	Negishi, E.	91
2000	Xerulin	Negishi, E.	80
2000	(±)-Harveynone	Negishi, E.	92
2000	(±)-Tricholomenyn A	Negishi, E.	92
2001	(–)-Salicylihalamides A and B	Fürstner, A.	93
2004	Ant venom	Organ, M. G.	94
2004	*cis*- and *trans*-Bupleurynol	Organ, M. G.	85
2004	6,7-Dehydrostipiamide	Negishi, E.	87

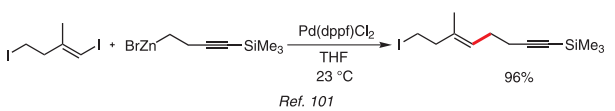
[a] A metabolite of *Cortinellus berkeleyanus*.



Scheme 3. The Pd-Catalyzed Alkenyl–Allyl Coupling in the Synthesis of Natural Products.



Scheme 4. The Pd-Catalyzed Coupling of Allenylzinc Derivatives.



eq 2

side reactions.[20] This usually makes Zn the metal of choice in the Pd-catalyzed benzyl–alkenyl coupling.

2.5.2. Allyl–Alkenyl and Alkenyl–Allyl Coupling Reactions for the Synthesis of 1,4-Pentadienes

Despite the fact that the reaction of allyl(tributyl)stannane with bromobenzene in the presence of $Pd(PPh_3)_4$, reported in 1977, is probably the first example of Pd-catalyzed allylation of organic halides,[96] the allyl–alkenyl coupling is generally to be avoided in favor of the alkenyl–allyl coupling for a couple of reasons. Firstly, allylmetals are generally prepared from the corresponding allyl halides. Their preparation with retention of regio- and stereochemistry is frequently quite challenging, generally more challenging than the preparation of the corresponding electrophiles. Secondly, allylmetals with a carbon–carbon double bond in the β,γ position tend to act as catalyst poisons more readily than benzylmetals. In this regard, allylmetals of low intrinsic nucleophilicity containing Sn and Si may be promising in the absence of other difficulties. This point largely remains to be experimentally established, however.

On the other hand, the Pd-catalyzed alkenyl–allyl coupling reactions of Zn, Al, and Zr alkenylmetals are generally favorable processes, even though unwanted allyl rearrangement accompanied by stereoisomerization can be a usually minor but potentially serious side reaction in cases where allyl groups are γ-mono- or β,γ-disubstituted. Allylic electrophiles are often so reactive toward Pd that allylic chlorides as well as a wide variety of oxygenated allyl derivatives, such as acetates, carbonates, phosphates, and even silyl ethers, are sufficiently reactive in this reaction. γ,γ-Disubstituted allyl derivatives can often be used with little or no sign of regio- and stereoisomerization. In marked contrast with the Tsuji–Trost allylation,[97] the Pd-catalyzed alkenyl–allyl coupling reactions proceed with clean stereoinversion at the allylic carbon center.[98]

The number of natural products synthesized by the Pd-catalyzed alkenyl–allyl coupling is still relatively small. Nonetheless, strictly regio- and stereospecific syntheses of α-farnesene and its 6*Z* isomer,[99] (+)-hennoxazole A,[100] as well as a series of coenzyme Q's and menaquinones,[101] persuasively point to its synthetic potential (**Scheme 3**). Both Pd and Ni complexes are highly satisfactory for catalyzing the alkenyl–benzyl and alkenyl–allyl coupling reactions.[99,101–103]

2.5.3. Pd-Catalyzed Allenylation and Propargylation

The Pd-catalyzed reactions of various types of organometals containing aryl, alkenyl, alkynyl, allenyl, and alkyl groups with either progargyl or allenyl electrophiles give predominantly or exclusively the corresponding allenes rather than alkynes.[1a] Generally, zinc appears to be the most satisfactory countercation among several others including Mg, Cu, Ag, B, Al, and Sn.[1a]

The Pd-catalyzed reaction of propargylmetals or allenylmetals is less predictable than the corresponding reaction of propargyl or allenyl electrophiles. Both 1,4-enynes and enallenes or arylallenes have been obtained, depending on the reactant structures and reaction conditions (**Scheme 4**).[104,105]

2.6. Alkyl–Alkenyl and Alkenyl–Alkyl Coupling Reactions

Alkyl halides and related electrophiles are substantially less reactive toward Pd than unsaturated organic electrophiles including those containing aryl, alkenyl, alkynyl, acyl as well as allyl, benzyl, and propargyl groups. The lower reactivity of alkyl halides toward Pd has been explained in terms of the lack of a proximal π bond. A difference in reactivity of at least a 100-fold between alkenyl

and alkyl iodides has been observed (**eq 2**).[101] Mainly for this reason, Pd-catalyzed alkylation of alkenyl derivatives has been achieved mostly via the alkyl–alkenyl coupling. However, alkyl halides are not inert towards Pd. For example, the use of highly nucleophilic Pd complexes containing bulky trialkylphosphines, such as $PCyp_3$(Cyp = cyclopentyl) and PCy_3 (Cy = cyclohexyl), has permitted the alkenyl–alkyl coupling between alkenylzinc derivatives and alkyl iodides, bromides, and tosylates.[56] Also noteworthy is the reaction of alkenylzirconium derivatives with alkyl bromides in the presence of 2.5 mol % of $Pd(acac)_2$ and LiBr (2 equiv) in THF–NMP.[106]

Despite recent promising developments such as those mentioned above, the Pd-catalyzed alkylation of alkenyl derivatives is still achieved mostly by the alkyl–alkenyl coupling protocol. In this regard, alkylzincs are generally superior to the other alkylmetals that have been examined to date, although alkylborons[107] and alkylmagnesiums[108] are satisfactory in many cases. In some reactions with alkenyl chlorides, Mg is even distinctly superior to Zn (**eq 3**).[29] Another noteworthy recent development is that alkylalanes generated in situ via Zr-catalyzed asymmetric carboalumination of alkenes can now be vinylated with vinyl bromide under the Zn–Pd double metal-catalyzed conditions in ca. 70% overall yields in one pot.[109] This reaction will be further discussed in Section 3.1. A similar hydrozirconation–cross-coupling tandem process is also promising.[110]

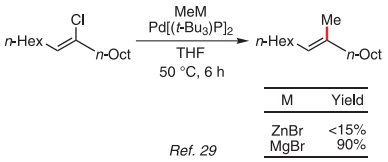
One should bear in mind that, in the Pd-catalyzed alkylation with alkylzincs or perhaps organozincs in general, the precise composition of alkylzincs, which significantly depends on the methods of their generation, affects the course of the subsequent cross-coupling process. One important determining factor is the alkyl/Zn/Li (or Mg) ratio. In a synthesis of (–)-discodermolide, it was shown to be desirable to add 3 equiv of *t*-BuLi to an alkyl iodide premixed with $ZnCl_2$ (**Scheme 5**).[111]

One potentially attractive recent development is a Pd-catalyzed asymmetric hydroboration–transmetallation (B→Zn)–alkenylation process producing chiral alkenes of 52–83% ee's.[112] If both the enantiomeric purity and the modest yields of 35–41% can be improved, it would prove to be a useful asymmetric synthetic tool. Presumably, the chiral borane intermediates are not sufficiently reactive in the desired Pd-catalyzed alkenylation, although no mention was made to this effect in the paper. The corresponding Pd-catalyzed acylation led to similar yields and stereoselectivities. These results, taken together with a previously developed Pd- or Ni-catalyzed vinylation of chiral benzylic secondary alkylmetals containing Mg or Zn,[1a] suggest that the development of a highly satisfactory and widely applicable Pd- or Ni-catalyzed asymmetric alkyl–alkenyl coupling might be imminent. A large number of natural products and related compounds have been synthesized by using the Pd-catalyzed alkenylation of alkylzinc derivatives (**Table 3**).[49,86,101,109,111,113–135]

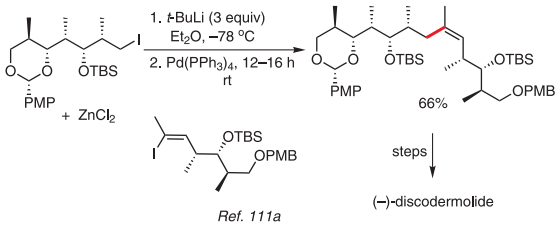
2.7. Acylation and Cyanation of Alkenyl Derivatives

2.7.1. Acylation of Alkenylmetals

The Pd-catalyzed reaction of a wide variety of organozincs with acyl chlorides[136] is one of the most generally applicable methods of acylation of organometals for the synthesis of ketones. Organozincs containing alkyl, aryl, alkenyl, and alkynyl groups have been successfully used. Particularly noteworthy are those cases where alkenyl- and alkynylzincs are utilized. α,β-Unsaturated ketones obtained as the products can, in principle, undergo competitive conjugate addition, as has been observed with organocoppers. However, this has not been a serious side reaction in the Pd-catalyzed acylation of alkenylzincs (**eq 4**).[136]



eq 3



Scheme 5. The Pd-Catalyzed Alkyl–Alkenyl Coupling with an Alkylzinc in a Total Synthesis of (–)-Discodermolide.

Table 3. Alkenylation of Alkylzinc Derivatives in the Synthesis of Natural Products and Related Compounds

Year	Natural Product	Major Author	Ref.
1980	Dendrolasin	Negishi, E.	113
1980	Mokupalide	Negishi, E.	113
1980	(2*E*,6*E*)-Farnesol	Negishi, E.	114
1987	(+)-Casbene	McMurry, J. E.	115
1989	(±)-Ageline A	Tokoroyama, T.	116
1989	Yellow scale pheromone	Millar, J. G.	117
1995	(–)-Discodermolide	Smith, A. B., III	111
1998	(+)-Amphidinolide J	Williams, D. R.	118
1999	Brevetoxin A	Nicolaou, K. C.	119
1999	(–)-Epothilone B	Schinzer, D.	120
1999	(+)-Pumiliotoxins A and B	Kibayashi, C.	121
2001	(*E*)- and (*Z*)-γ-Bisabolenes	Negishi, E.	49
2001	(–)-4a,5-Dihydrostreptazolin	Cossy, J.	122
2001	Mycolactones A and B	Kishi, Y.	123
2002	Coenzymes Q_3 and Q_{10}	Negishi, E.	101
2002	*trans*-Epothilone A	Altmann, K. H.	124
2002	(2*E*,6*Z*), (2*Z*,6*Z*), and (2*Z*,6*E*)-Farnesols	Negishi, E.	101
2002	(2*E*,6*Z*,10*E*)-Geranylgeraniol	Negishi, E.	101
2002	Menaquinone-3	Negishi, E.	101
2002	Oleandolide	Panek, J. S.	125
2002	Sphingofungin F	Ham, W.-H.	126
2002	Ionomycin	Lautens, M.	127
2003	Borrelidin	Morken, J. P.	128
2003	Delactonmycin	Pilli, R. A.	129
2004	(–)-Callystatin A	Panek, J. S.	86
2004	Capensifuranone	Williams, D. R.	130
2004	(+)-Murisolin	Curran, D. P.	131
2004	Scyphostatin side chain	Negishi, E.	132
2004	Scyphostatin	Katoh, T.	133
2004	Siphonarienal	Negishi, E.	134
2004	Siphonarienolone	Negishi, E.	134
2004	Siphonarienone	Negishi, E.	134
2005	Ionomycin (a key intermediate of)	Negishi, E.	109
2005	Borrelidin (a key intermediate of)	Negishi, E.	109
2005	Preen gland wax of graylag goose *Anser anser*	Negishi, E.	135

Although the Pd-catalyzed acylation of organozincs has been applied to the synthesis of several natural products, none involves a Pd-catalyzed alkenylation. A few interesting variants of the Pd-catalyzed acylation of organozincs have also been developed. In one of them, thiol esters are employed in place of acyl chlorides.[137] This reaction has been applied to the synthesis of at least one α,β-unsaturated enone, 1-(4-methoxyphenyl)-4-nonen-3-one, in 79% yield.[137b] However, it is not readily apparent what advantage this reaction offers over the corresponding reaction with the acid chloride, from which the required thiol ester is prepared.

A few other more recent variations on the Pd-catalyzed acylation of organozincs include the Pd- or Ni-catalyzed reactions of organozincs with carboxylic anhydrides[138,139a–c] and acyl fluorides.[139d] In one procedure, carboxylic anhydrides are generated in situ from alkali metal carboxylates and $ClCO_2Et$.[138] Desymmetrization of symmetrical anhydrides under the influence of a chiral ligand appears to be promising. However, no examples are known in which alkenylzincs were used.

2.7.2. Cyanation of Alkenyl Electrophiles

The cyanation of alkyl halides with alkali metal cyanides and that of aryl halides with a stoichiometric amount of CuCN, i.e., the Rosenmund–Von Braun reaction, represent classic C–C bond-forming reactions. Their transition-metal-catalyzed counterpart was first reported by Takagi.[140a] Under modified conditions, the reaction has also been applied to the cyanation of alkenyl electrophiles.[141,142] Over the past decade or so, the use of other metal countercations and other reaction parameters has made the Pd-catalyzed cyanation more widely applicable. In particular, aryl bromides and even chlorides can now be satisfactorily cyanated with $Zn(CN)_2$ in DMF or DMA in the presence of Pd catalysts containing PPh_3, dppf, or other phosphines (**eq 5**).[1a,143,144] However, despite extensive recent developmental work, little, if any, has been published on the cyanation of alkenyl electrophiles with $Zn(CN)_2$.

2.8. α Alkenylation of Metal Enolates and α-Halo-α,β-unsaturated Carbonyl Compounds

The alkenylation, arylation, and alkynylation of α-halo- and β-halo-α,β-unsaturated carbonyl compounds are highly desirable synthetic operations.[145] The coupling with β-halo-α,β-unsaturated carbonyl compounds is a fundamentally very favorable process and has been termed *conjugate substitution*. Its Pd-catalyzed version, reported first in 1976,[17] has since been extensively developed and applied to the synthesis of natural products and other organic compounds.[1a] On the other hand, the corresponding reaction of α-halo-α,β-unsaturated carbonyl compounds has proved to be much more demanding.[145b] Since the classical method of α substitution of carbonyl compounds by C–C-bond-forming reactions of enolates had until recently been practically limited to α substitution with alkyl groups, it was very desirable to overcome this critical limitation. Fortunately, all three classes of unsaturated carbon atom (alkenes, alkynes, and arenes) can be accommodated, in principle, by various protocols of Pd- or Ni-catalyzed α substitution of carbonyl compounds. One of the two most widely investigated protocols is the direct α substitution of metal enolates catalyzed by Pd or Ni complexes (Pd- or Ni-catalyzed *direct α substitution* of metal enolates).[1a] This is clearly one of the most straightforward, efficient, and desirable approaches. In many demanding and delicate cases, however, this approach frequently suffers from difficulties associated with several aspects of the reaction most notably regioselectivity. To cope with difficulties pertaining to regiochemical control, an alternate approach involving Pd- or Ni-catalyzed α substitution of α,β-unsaturated carbonyl compounds and related derivatives (Pd- or Ni-catalyzed *indirect α substitution* via α substitution of α-halo-α,β-unsaturated carbonyl compounds) has been developed.[1a,145b] The relationship between these two methods is shown in **Scheme 6**.[146] Since α,β-unsaturated carbonyl compounds often serve as precursors to regiodefined enolates, their use as the starting carbonyl compounds in the latter approach is readily justified. Their α halogenaton amounts to an additional step in comparison with the direct α substitution of regiodefined enolates derived from α,β-unsaturated enones. In many cases, however, the need for this extra step may be more than justified by (i) being able to strictly control the regiochemistry of the α substitution, and (ii) generally more favorable C–C-bond formation through the use of α-halo-α,β-unsaturated carbonyl compounds than by direct α substitution of enolates. Furthermore, in cases where α-substituted α,β-unsaturated carbonyl compounds are the desired final products, the latter protocol with α-halo-α,β-unsaturated carbonyl compounds should prove to be more advantageous than the α substitution of enolates. Although different, a related Pd-catalyzed α alkenylation of α-hetero-substituted β,γ-unsaturated carbonyl compounds is also noteworthy (**Scheme 7**).[147]

Both types of α substitution reactions reported before 2000 have been systematically and comprehensively discussed.[1a] Some of the more recent examples of the application to natural product synthesis[74,92,148,149] of the Pd-catalyzed α substitution of α-halo-α,β-unsaturated carbonyl compounds with alkenyl- and alkynylzincs, are shown in **Scheme 8**.

3. Special Topics of the Pd-Catalyzed Alkenylation

3.1. Pd-Catalyzed Hydrometallation–Cross-Coupling and Carbometallation–Cross-Coupling Tandem Reactions

The hydrometallation–cross-coupling and carbometallation–cross-coupling tandem reactions, with or without the use of $ZnBr_2$ or $ZnCl_2$ as a cocatalyst,[16,17,21–24] have played a major role in the Pd-catalyzed alkenylation involving Zn, Al, and Zr as well as B, Sn, and Cu. These "one-pot" procedures not only are step-economical, but also permit minimization of the use of cost-adding iodination or bromination and subsequent lithiation or other metallation reactions. In pursuit of highly satisfactory syntheses of alkenes via the Pd-catalyzed alkenylation, iterative procedures involving a minimum number of steps in each cycle, preferably one, have been recognized as being highly desirable in the syntheses of terpenoids, carotenoids, polypropionates, and other natural products containing oligomeric structural units. In this section, some of the noteworthy advances in this area, achieved mainly over the past decade, are presented with a focus on their applications to the synthesis of natural products.

3.1.1. Hydrozirconation–Cross-Coupling Tandem Reactions of 2-Alkynes

Whereas terminal alkynes can be hydrometallated highly regioselectively (typically >98%) with metal hydrides containing B, Al, and Zr, the corresponding reactions of internal alkynes are generally less regioselective.[150,151] However, the hydrozirconation with $HZrCp_2Cl$, which contains not only bulky ligands but also a transition metal, can be more readily equilibrated under thermal conditions in the presence of an excess of $HZrCp_2Cl$ than the corresponding reactions with boron and aluminum hydrides. Thus, the regioselectivity observed with 2-alkynes containing secondary alkyl groups can be improved to nearly 100% (**Scheme 9**).[84,151,152] This procedure has been applied to the synthesis of some natural products, such as reveromycin B[78] and motuporin[84] (**Scheme 10**).

3.1.2. Iterative Tandem Carboalumination–Vinylation for the Asymmetric Synthesis of Reduced Polypropionates

The Zr-catalyzed asymmetric carboalumination reaction (ZACA reaction) of terminal alkenes[48,152] can be followed by (i) oxidation with O_2; (ii) iodination with I_2, PPh_3, and imidazole; and (iii) lithiation with *t*-BuLi, zincation with $ZnBr_2$ or $ZnCl_2$, and Pd-catalyzed vinylation to produce another terminal alkene, which can be subjected to another round of this three-step cycle.[153] This catalytic three-step process has been successfully applied to efficient, catalytic, and asymmetric syntheses of reduced polypropionates and related compounds, such as siphonarienal,[128] siphonarienone,[128] siphonarienolone,[128] and the scyphostatin side chain.[127]

The long-pending problem of how to carry out alkene hydroalumination, to generate alkylalanes, and directly achieve their Pd- or Ni-catalyzed cross-coupling has recently been overcome in the case of vinylation.[109] This development has permitted iteration of the one-pot procedure for the unprecedentedly efficient and asymmetric construction of the reduced polypropionate segments of ionomycin and borrelidin (**Scheme 11**).[109]

3.1.3. Iterative Carboalumination–Pd-Catalyzed Alkylation for the Synthesis of Terpenoids Containing 1,5-Diene Units

Although no one-pot carbometallation–cross-coupling tandem process is involved, an iterative two-step homologation procedure for the synthesis of terpenoids containing 1,5-diene units, such as mokupalide was developed as early as 1980.[113]

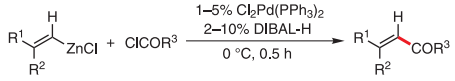
In many cases where there are three or more isoprene units in the target molecule, it would be more efficient to devise iterative procedures involving one-step incorporation of one isoprene unit.[47] This has been successfully applied to the synthesis of coenzymes Q_n (n = 3,10), menaquinone 3, the less commonly encountered (2*E*,6*Z*)- and (2*Z*,6*Z*)-farnesols, and even (2*E*,6*Z*,10*E*)-geranylgeraniol (**Scheme 12**).[101] The formation of undesired stereoisomers was not detected in all of these syntheses, although successful synthetic designs must carefully avoid the potentially competitive formation of byproducts, such as cyclopropylcarbinyl derivatives, and pay extra care to the use of the potentially more capricious (*Z*)-1,4-diiodo-2-methyl-1-butene.[109]

3.2. Pd-Catalyzed Double Alkenylation Using 1,1-Dihalo-1-alkenes and Related Compounds

As discussed throughout Sections 2 and 3.1, the regio- and stereoselective hydrometallation of internal alkynes and carbometallation of terminal alkynes provide convenient and selective routes to trisubstituted alkenes. Even so, there are many instances of trisubstituted alkenes, where new and alternate synthetic routes are desirable. Three related classes of 1,1-disubstituted 1-alkenes (**Figure 3**) have collectively provided some useful routes to trisubstituted alkenes. The discussion in this section will focus mainly on the selective and stepwise Pd-catalyzed double cross-coupling of 1,1-dihalo-1-alkenes and their use in natural product synthesis.

3.2.1. Pd-Catalyzed Double Cross-Coupling Reactions of 1,1-Dihalo-1-alkenes with Zn, Al, and Zr Organometals

The palladium-catalyzed trans-selective monoarylation of 1,1-dichloro-1-alkenes with arylmagnesium derivatives was first reported in 1987.[154] Several examples of a second Pd-catalyzed arylation, also with arylmagnesium derivatives, were presented



R^1	R^2	R^3	Yield	Stereoselectivity
n-Pent	H	Me	76%	>99% *E*
n-Hex	H	MeO	56%	>98% *E*
n-Hex	Me	Me	77%	>98% *E*

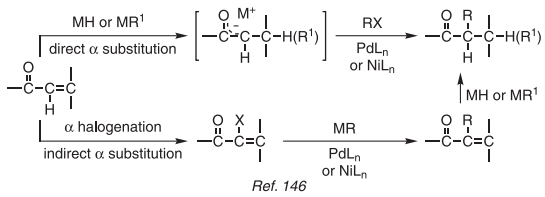
Ref. 136

eq 4

Ar = aryl; X = I, Br, Cl
PdL_n = $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, others

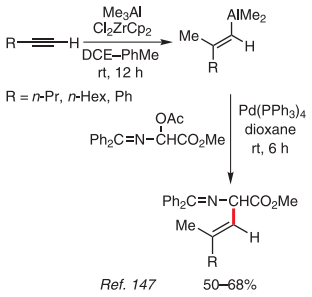
Ref. 143,144

eq 5



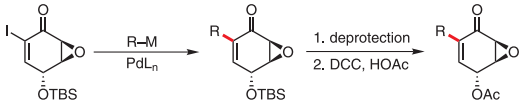
Ref. 146

Scheme 6. Pd- or Ni-Catalyzed Direct α Substitution vs. Indirect α Substitution.



Ref. 147 50–68%

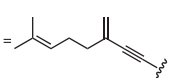
Scheme 7. Pd-Catalyzed α Alkenylation of α-Imino-α-acetoxyacetates.



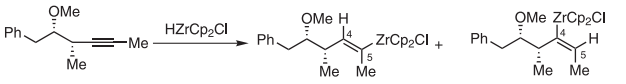
M	PdL_n	Cond.	Yield[a]	Ref.
ZnBr	$Pd(dba)_2$,TFP	DMF, 25 °C, 1 h	80%	92
$SnBu_3$	$Cl_2Pd(PPh_3)_2$	CuI, NMP	39%	148b
H	$Cl_2Pd(PPh_3)_2$	CuI, $(i\text{-Pr})_2NH$	54%	149

[a] Yield of the cross-coupling step.

(±)-tricholomenyn A



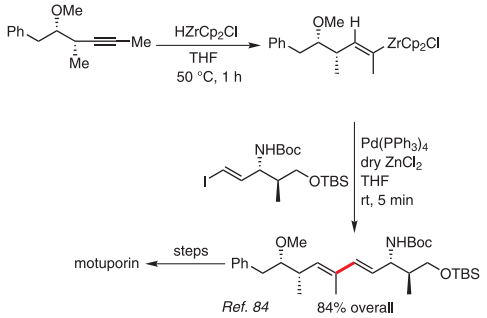
Scheme 8. Pd-Catalyzed α Alkenylation and α Alkynylation of α-Iodo-α,β-unsaturated Carbonyl Compounds in Natural Product Synthesis.



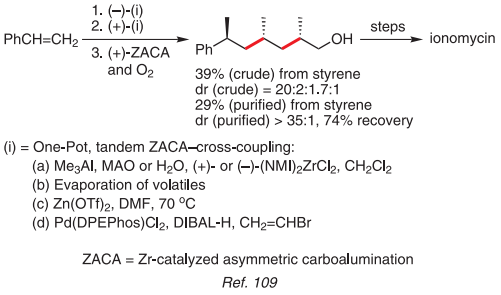
Equiv. of $HZrCp_2Cl$	Solvent	Temp.	Time	C(Zr)-5/C(Zr)-4
1.5	PhH	45 °C	0.3 h	75:25
2.0	PhH	50 °C	4 h	100:0
2.0	THF	50 °C	1 h	100:0

Ref. 84c

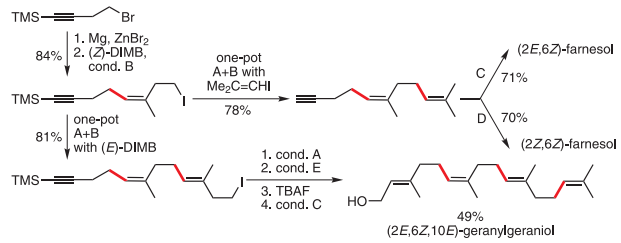
Scheme 9. Improvement of the Regioselectivity of the Hydrozirconation of 2-Alkynes.



Scheme 10. The Synthesis of Natural Products by the Hydrozirconation of 2-Alkynes Followed by Cross-Coupling.



Scheme 11. Iterative One-Pot Homologation of Reduced Polypropionates via ZACA–Pd-Catalyzed Vinylation.



Scheme 12. Iterative One-Pot Homologation of Terpenoids Containing 1,5-Diene Units with (*E*)- and (*Z*)-1,4-Diiodo-2-methyl-1-butenes.

in the same paper. In the only example of trans-selective monoalkylation reported in the same paper, the use of *n*-BuMgBr did not give the desired product at all, but that of *n*-BuZnCl led to the desired monobutylated product, *trans*-2-chloro-1-phenyl-1-hexene, in 81% yield. The Pd-catalyzed second alkylation of this monobutylated intermediate with *n*-HexMgBr gave the desired trisubstituted alkene with full retention of configuration in 77% yield. Evidently, the first-stage alkylation was strongly aided by the fact that the starting compound was β,β-dichlorostyrene, since attempts to achieve a related trans-selective monoalkylation of 2-alkyl-substituted 1,1-dichloro- or 1,1-dibromo-1-alkenes under the same conditions failed.[154]

Many subsequently published papers reported Pd-catalyzed trans-selective monosubstitution reactions of 1,1-dichloro- and 1,1-dibromo-1-alkenes with arylzincs,[155] alkenylzincs,[77,156a] alkenylzirconiums,[77] alkenylborons,[157] aryl- and vinylstannanes,[158] and alkynes in the presence of CuI and a base.[156b,159] However, the scope of the second substitution via Pd-catalyzed cross-coupling to produce trisubstituted alkenes had until recently been essentially limited to a few examples. In particular, there was only one example of methylation in the second step of the disubstitution of an apparently highly activated β,β-dibromostyrene derivative.[158]

With the goal of developing Pd-catalyzed, stepwise double substitution procedures that are well-suited for the synthesis of various types of natural product, a series of systematic investigations have been conducted, which focused on the Pd-catalyzed trans-selective single-stage arylation, alkenylation, or alkynylation of 2-alkyl-substituted 1,1-dihalo-1-alkenes—followed by a second-stage alkylation, especially methylation and ethylation (**Scheme 13**).[160–162] These investigations led to the following noteworthy findings:

- Both 1,1-dichloro- and 1,1-dibromo-1-alkenes, readily obtainable from the corresponding aldehydes, can be selectively monosubstituted (≥98% trans) in good yields with aryl-, alkenyl-, and alkynylzinc reagents by using $Pd(DPEphos)Cl_2$ as catalyst. Alkynylzincs are generally superior to terminal alkynes used in conjunction with a catalytic amount of CuI and $(i\text{-}Pr)_2NH$, especially in cases where 1,1-dichloro-1-alkenes are employed.
- In the second-step substitution, alkylation with alkylmetals, such as Me_2Zn, Et_2Zn, and higher homologues, can be achieved in excellent yields by using $Pd[(t\text{-}Bu)_3P]_2$ as catalyst. Under these conditions, little or no alkene stereoisomerization is observed.
- Perhaps, the most striking finding in this series of investigations is that the second-stage alkylation in the presence of $Pd(DPEphos)Cl_2$ or those Pd complexes containing more conventional phosphines, such as dppf, PPh_3, or TFP, is often accompanied by nearly complete stereoinversion of the initially dihalo-bearing double bond.[163] With DPEphos and dppf, ≥97% stereoinversion has been observed in many cases.

1,1-Dihalo-1-alkenes containing a 2-alkenyl or 2-alkynyl group do not undergo stereoinversion at all, whereas the presence of an aryl group in the same position induces partial stereoisomerization. Chelation of Pd by a π bond in the γ,δ position must inhibit stereoinversion. Although the mechanism of this interesting stereoinversion is still unclear at this time, stereoinversion via a π–σ–π rearrangement—widely accepted as the mechanism for stereoinversion of allylmetals—must not be operative, as this mechanism must invariably proceed with double inversions, which were not observed. The mechanism shown in **Scheme 14**, on the other hand, appears to be not only compatible with the observed facts, but also very plausible.

Irrespective of mechanistic details, the synthesis of either *E*,*E* or *Z*,*E* conjugated dienes from the same starting compounds in a high-yielding and stereoselective manner should be of considerable synthetic utility, as suggested by a recent synthesis of (–)-callystatin A.[86]

3.2.2. Synthesis of Unsymmetrically Substituted Conjugated Diynes via Pd-Catalyzed Alkenylation with 1,1-Dichloroethylene

Unsymmetrically substituted conjugated diynes have been prepared most commonly by the Cu-catalyzed alkynyl–alkynyl coupling called the Cadiot–Chodkiewicz reaction.[164] This synthesis requires two steps from the two terminal alkynes to be coupled, including the conversion of one or the other alkyne into the corresponding 1-haloalkyne. The main limitation of this method is that the reaction tends to produce rather frequently a mixture of the desired diyne and two unwanted symmetrically substituted diynes.[164] This difficulty has also been observed in the corresponding Pd-catalyzed alkynyl–alkynyl coupling, although some very favorable cases are known. A strictly "cross-selective" route to conjugated diynes via a Pd-catalyzed monoalkynylation of 1,2-dihaloethylenes[165,166] has been devised as a superior alternative, as discussed in Section 3.3. Although highly selective and widely applicable, this reaction suffered from the high cost of the 1,2-dihaloethylenes starting materials. To overcome this drawback, an alternative method that starts with 1,1-dichloroethylenes was developed. It has long been known that the Pd-catalyzed monoalkynylation of inexpensive vinylidene chloride gives 2-chloro-1-en-3-ynes in excellent yields provided that 5 equiv of vinylidene chloride is used.[167] This reaction has been applied in a highly satisfactory and economical synthesis of unsymmetrically substituted conjugated diynes (**Scheme 15**).[168]

3.2.3. 1,1-Dimetallo-1-alkenes and 1-Hetero-substituted 1-Alkenylmetals in the Pd-Catalyzed Alkenylation

The hydrometallation and carbometallation of 1-metallo-1-alkynes are often highly regio- and stereoselective, producing 1,1-dimetallo-1-alkenes mostly via syn addition. In cases where the two metals in 1,1-dimetallo-1-alkenes are sufficiently different, monohalogenation and monosubstitution with other heteroatoms can give 1-heterosubstituted 1-alkenylmetals. These 1,1-disubstituted alkenes can, in principle, be converted into various trisubstituted alkenes via a Pd- or Ni-catalyzed cross-coupling. Even though reactions of this class of compounds have been used in the synthesis of temarotene (**Scheme 16**)[169] and discodermolide,[170] the current scope of highly satisfactory and synthetically useful applications appears to be still rather limited. This, however, is potentially a promising field for exploration and development.

3.3. Pd-Catalyzed Alkenylation Utilizing 1,2-Dihalo-1-alkenes and Related Compounds

1,2-Dihaloethylenes are, in principle, a group of attractive synthetic modules or synthons. Even if one considers only Cl, Br, and I, there are six each of (*E*)- and (*Z*)-1,2-dihaloethylenes. Of these, (*E*)-ClCH=CHCl, (*Z*)-ClCH=CHCl, (*E*)-BrCH=CHBr, and (*E*)-BrCH=CHI are commercially available. (*E*)-ClCH=CHI, which is already synthetically useful, might be commercialized in the near future. On the other hand, the synthetic value of ICH=CHI and BrCH=CHCl is not clear at this point. Some of the earlier contributions, mostly by the Linstrumelle–Alami group[171] and that of Rossi,[172] have been reviewed.[1a] In these studies, (*E*)- or (*Z*)-ClCH=CHCl and *E*/*Z* mixtures of BrCH=CHBr were used. An

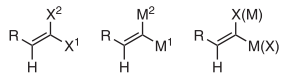
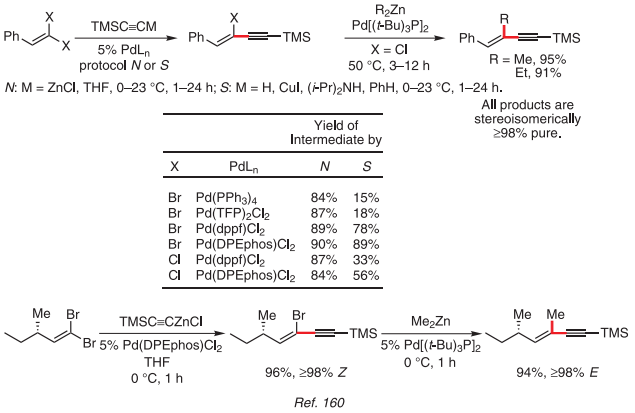
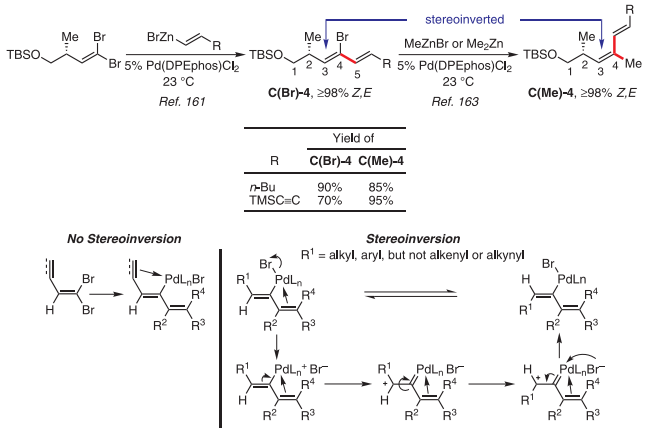


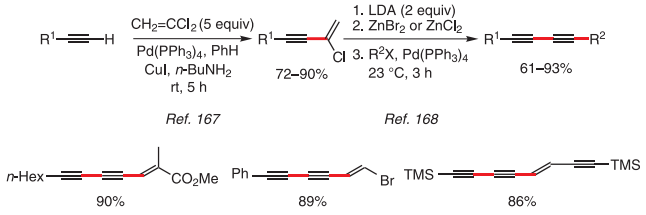
Figure 3. 1,1-Dihalo-1-alkenes and Related Compounds.



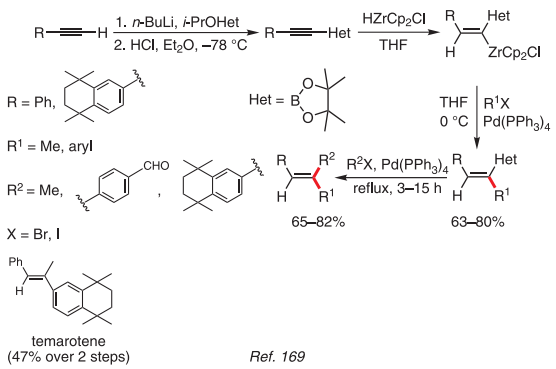
Scheme 13. Pd-Catalyzed Selective and Stepwise Disubstitution of 1,1-Dihalo-1-alkenes with Organozincs.



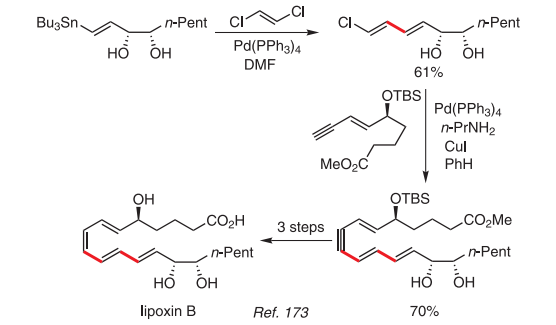
Scheme 14. Pd-Catalyzed *E*⇌*Z* Isomerization of 2-Pallado-1,3-dienes.



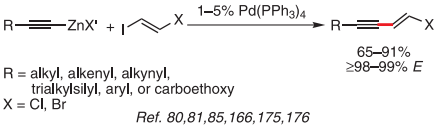
Scheme 15. The Pd-Catalyzed, Strictly "Pair-Selective", Two-Step Synthesis of Unsymmetrically Substituted Conjugated Diynes.



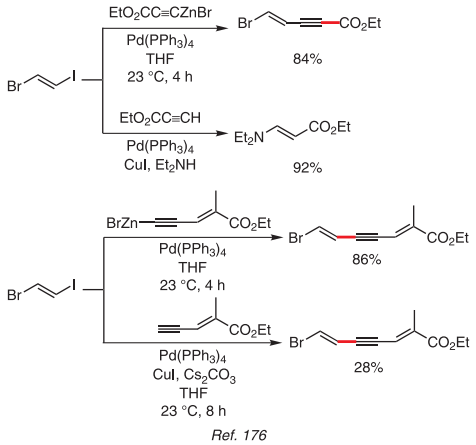
Scheme 16. The Pd-Catalyzed Two-Stage Cross-Coupling with 1-Bora-1-zircona-1-alkenes.



Scheme 17. The Synthesis of Lipoxin B via a Pd-Catalyzed Alkenylation and Alkynylation of (*E*)-ClCH=CHCl.



eq 6



Scheme 18. Comparison of the Negishi and Sonogashira Coupling Reactions in the Pd-Catalyzed Alkynylation of (*E*)-BrCH=CHI.

excess (≤5 equiv) of the 1,2-dihaloethylene was typically needed to attain high monosubstitution and/or trans-selectivity levels. Nonetheless, some of these reactions appear to be highly promising, as suggested by the synthesis of lipoxin B (**Scheme 17**).[173] Also attractive and promising are some cyclization reactions via Pd-catalyzed alkynyl–alkenyl coupling using (*Z*)-ClCH=CHCl.[15,174] The discussion in this section will focus, however, on the use of (*E*)-ClCH=CHI, (*E*)-BrCH=CHI, and (*E*)-BrCH=CHC≡CSiMe$_3$, which is derived from (*E*)-BrCH=CHI.

3.3.1. Pd-Catalyzed Selective Monosubstitution of (*E*)-2-Chloro- and (*E*)-2-Bromo-1-iodoethenes

The presence of the second halogen atom in 1,2-dihalo-1-alkenes renders these compounds significantly more reactive than ordinary monohaloalkenes in their Pd-catalyzed monosubstitution reactions. Less well appreciated is that the second substitution of the monosubstitution products derived from 1,2-dihaloalkenes is also substantially more favorable than the corresponding reaction of the same monohaloalkenes in their free alkene forms. After all, the initial products of monosubstitution are monohaloalkene–Pd complexes ready for the second oxidative addition via a strictly intramolecular process. For these reasons, any of the 1,2-dihalo-1-alkenes containing Cl, Br, and/or I are sufficiently reactive in the Pd-catalyzed cross-coupling. Indeed, the main concern in their Pd-catalyzed monosubstitution is how to prevent an unwanted second substitution. This is precisely the reason why a large excess of ClCH=CHCl is commonly used to minimize unwanted disubstitution. Although not fully established, this difficulty may be expected to be further magnified in the cases of BrCH=CHBr and ICH=CHI. Little, if any, is known about BrCH=CHCl. In ClCH=CHI, two carbon–halogen bonds are maximally differentiated, and monosubstitution of the iodine is expected to be more favorable. On the other hand, the second substitution of the chloroalkene products with a different organometal than the one used for the first substitution is generally less favorable than the corresponding reaction of bromoalkenes. In this respect, BrCH=CHI is a more desirable reagent than ClCH=CHI. It would be advantageous to consider both BrCH=CHI and ClCH=CHI and then compare the overall results for optimization. In cases where the cost of these 1,2-dihaloethylenes is a significant factor, ClCH=CHCl may also be tested and compared. In contrast to the Pd-catalyzed cross-coupling of ordinary monohaloalkenes, the corresponding monosubstitution of 1,2-dihaloethylenes has proved to be generally much more capricious and unpredictable. Nevertheless, the Pd-catalyzed monoalkynylation of (*E*)-ClCH=CHI and (*E*)-BrCH=CHI has been developed into a dependable and widely applicable reaction (**eq 6**).[80,81,85,166,175,176] In this regard, some striking differences between the use of alkynylzincs and terminal alkynes containing electron-withdrawing groups should be noted (**Scheme 18**).[176]

As expected, the Pd-catalyzed alkenylation of (*E*)-ClCH=CHI was favorable,[60,79] but the corresponding reaction of (*E*)-BrCH=CHI required extensive optimization. After screening many catalysts and reaction parameters, a set of parameters consisting of $InCl_3$ (≤0.34 equiv), 1% Pd(DPEphos)Cl_2, 2% DIBAL-H, 2% TFP, and THF was found to be almost uniquely satisfactory (yields of the monoalkenylated products ranged from 77 to 91%).[60] This has also been applied to the related arylation; however, the corresponding alkylation has not been satisfactory.

The 1-chloro- and 1-bromoalkenes, obtained as described in the preceding two paragraphs, rarely represent the final natural products. However, pitiamide A is one such rare example, which has been prepared by using this approach.[79]

3.3.2. Pd-Catalyzed Second-Stage Substitution Reactions of Alkenyl Chlorides and Bromides, and the One-Pot Tandem Disubstitution of 1,2-Dihaloethylenes

Even though 1-chloro-1-en-3-ynes and 1-chloro-1,3-dienes, obtained as described in Section 3.3.1, are considerably more reactive than 1-chloro-1-monoenes in the Pd-catalyzed cross-coupling due to the presence of conjugated π bonds, their Pd-catalyzed cross-coupling reactions are significantly more sluggish than the corresponding reactions of their bromo analogs. Nevertheless, a highly satisfactory (71–97% yields) set of conditions has recently been found for their alkylation and arylation.[177] It consists of the use of alkyl- or arylmagnesium halides, $ZnCl_2$ (0.6 equiv), 5% $Pd(dppf)Cl_2$, and THF at reflux temperature. This development has significantly elevated the synthetic value of (*E*)-ClCH=CHI and (*E*)-ClCH=CHCl vis-à-vis (*E*)-BrCH=CHI.

The Pd-catalyzed disubstitution of (*E*)-ClCH=CHI and (*E*)-BrCH=CHI can be achieved without isolation of the monosubstitution products, as exemplified by the Pd-catalyzed one-pot dialkynylation.[176] Construction of the pentaenediyne framework of xerulin was achieved by a Pd-catalyzed two-step alkynylation–alkenylation.[80] A similar Pd-catalyzed alkynylation–alkenylation of (*E*)-BrCH=CHI has been applied to the synthesis of *cis*- and *trans*-bupleurynols (**Scheme 19**).[85]

A useful variation of the Pd-catalyzed alkynylation–alkenylation of (*E*)-BrCH=CHI is to use its C–I bond as an electrophile but convert the C–Br bond into a nucleophilic C–Zn bond, as in the preparation of ethyl 2-methyl-2,4-heptadien-6-ynoate, a key intermediate in the synthesis of 6,7-dehydrostipiamide.[87]

3.3.3. Iterative Carbon–Carbon-Bond Formation by the Pd-Catalyzed Cross-Coupling of 1,2-Dihaloethylenes and 1-Halo-1-buten-3-ynes

1,2-Dihaloethylenes and 1-halo-1-buten-3-ynes discussed above can be used as two- and four-carbon synthons, respectively, for the iterative construction of carbon skeltons containing repeating units derived from them. In the synthesis of xerulin,[80] an iterative process was utilized to synthesize a bromodiendiyne as a key intermediate. It should also be noted that this procedure can, in principle, be iterated as many times as desired. Although this process has not yet been applied to the synthesis of conjugated triynes or higher oligoynes, it has been employed for the synthesis of various conjugated diynes.[165,166] It is a satisfactory and strictly "pair-selective" method, but a potentially more economical diyne synthesis, shown in Scheme 15, could prove to be more economical in most cases.

One highly attractive application of (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne is to use it as a four-carbon synthon for the iterative construction of conjugated oligoenes including oligoene macrolides, carotenoids, and retinoids. A highly efficient, selective, and general method for the synthesis of conjugated (*all-E*)-oligoenes of type $(CH=CH)_n$ via an iterative tandem hydrozirconation–palladium-catalyzed cross-coupling has recently been developed (**Scheme 20**).[178] It promises to be applicable to the efficient synthesis of various oligoene macrolides.[179]

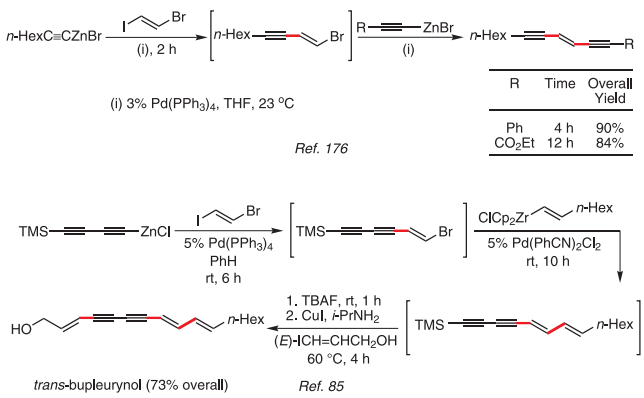
A related iterative carboalumination–cross-coupling process has also been developed and applied to the synthesis of both symmetrical and unsymmetrical carotenoids as well as retinoids.[81] It is not only highly efficient but also ≥98–99% stereoselective, even after incorporation of several stereodefined trisubstituted alkene units along with similar numbers of disubstituted alkene units.

3.3.4. 1,2-Dimetalloethylenes, 1-Metallo-2-haloethylenes, and Other Related Alkene Synthons

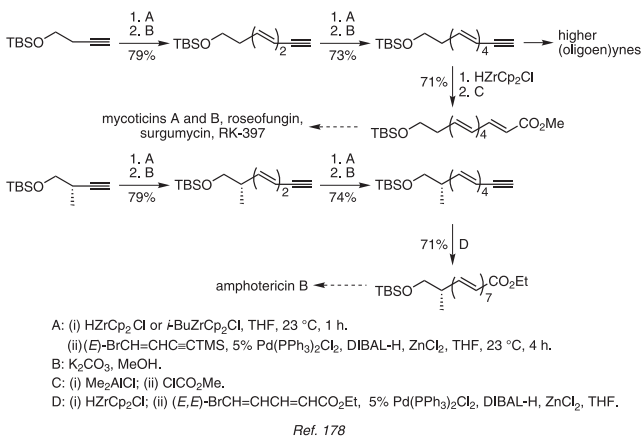
A number of classes of 1,2-dimetalloethylenes and 1,2-dimetallo-1-alkenes are conceivable, and some of those that contain Zn, B, Si, and Sn were briefly discussed in Section 2.2.1.[1a] In Scheme 1, (*E*)-$Bu_3SnCH=CHZnCl$ is shown to be far superior to (*E*)-$Bu_3SnCH=CHSnBu_3$ in the Pd-catalyzed reaction with methyl (*E*)-3-bromo-2-methylacrylate.[30] A related (*all-E*)-1,3,5-hexatriene derivative was recently used to synthesize xerulinic acid (**Scheme 21**).[88]

4. Conclusions

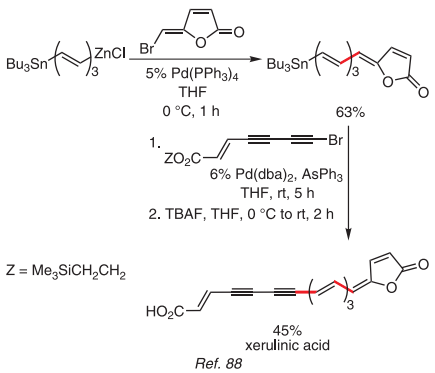
- Since the discovery of the Pd-catalyzed alkenylation by the Negishi coupling in the mid-1970s,[16–18,21–24] it has been extensively developed into a widely applicable, highly selective, and generally satisfactory method for the synthesis of alkenes by attaching a C–C single bond onto a C=C moiety.
- Generally speaking, zinc offers a very desirable combination of (i) high reactivity under the Pd-catalyzed conditions and (ii) a surprisingly favorable chemoselectivity profile. Furthermore, zinc salts, such as $ZnCl_2$ and $ZnBr_2$, can be used as promoters in the Pd-catalyzed cross-coupling reactions of other organometals including those containing Li, Mg, B, Al, Sn, Cu, and Zr primarily through transmetallation to Zn (Scheme 1). This has effectively expanded the scope of the Pd-catalyzed organozinc cross-coupling. In some cases of alkenylation with alkenylmetals containing Al and Zr, however, $InCl_3$ and $InBr_3$ can be more favorable promoters than Zn salts.[60] It is also worth noting that organomagnesiums, which are generally inferior to the corresponding organozincs, may prove to be superior to the latter, as suggested by recent results obtained with certain alkenyl chlorides.[29] It is not inconceivable that the hard and soft acids and bases principle is operative in the Pd-catalyzed cross-coupling as well.
- Until recently, the great majority of the Negishi coupling examples had been carried out in the presence of Pd catalysts containing PPh_3, TFP, dppf, and dppp. More recent studies have indicated that those containing DPEphos, trialkylphosphines (e.g., $P(t\text{-}Bu)_3$, PCy_3, $PCyp_3$), and 2-dialkylphosphinobiphenyls, as well as some non-phosphine ligands, are not only useful in many demanding cases, but also complementary among themselves (Figure 1 and Schemes 13 and 14). It is important to note that, although these structurally more varied and/or complex ligands will add to the cost of carrying out the Pd-catalyzed cross-coupling, higher costs of ligands and catalysts can be offset by more favorable results, in particular by higher turnover numbers (TONs). In this context, it is encouraging to learn from recent studies that the TONs in the Pd-catalyzed cross-couplings, including the Negishi coupling, can generally and readily reach the 10^3–10^5 levels and even the $>10^6$ levels in some cases.[61]
- Of the sixteen cross-coupling combinations for the Pd-catalyzed alkenylation discussed throughout this article, only four classes of reaction, namely allyl–alkenyl, propargyl–alkenyl, enoxy–alkenyl, and alkenyl–alkyl coupling reactions remain underdeveloped. Fortunately, allyl–alkenyl, propargyl–alkenyl, and alkenyl–alkyl coupling reactions may be substituted with the corresponding alkenyl–allyl, alkenyl–propargyl, and alkyl–alkenyl coupling reactions to attain the same synthetic goals in most cases. α Alkenylation of carbonyl compounds can also be achieved via the Pd-catalyzed reaction of alkenylzincs with α-haloenones (Section 2.8). Thus, the



Scheme 19. The Pd-Catalyzed Dialkynylation and Alkynylation–Alkenylation of (*E*)-BrCH=CHI.



Scheme 20. The Synthesis of Conjugated Oligoenes via an Iterative Hydrozirconation–Cross-Coupling Tandem Process.



Scheme 21. The Synthesis of Xerulinic Acid via an Alkenyl–Alkenyl Coupling with (*all-E*)-6-Stanna-1,3,5-hexatrienylzinc Chloride.

Pd-catalyzed alkenylation can, in principle, be employed for the synthesis of all conceivable types of alkenes. The Pd-catalyzed alkenylation by the Negishi coupling is not only generally favorable in twelve out of sixteen cross-coupling combinations for the synthesis of alkenes, but also either the most satisfactory or one of the most satisfactory cross-coupling protocols known today along with the Pd-catalyzed alkenylation via alkenylborons (Suzuki coupling).[1,5,6] Some of the other currently known protocols involving Mg,[9,10] In,[11] Si,[1,12] and Cu[13] may also be further developed into widely used ones. Especially noteworthy are the alkenyl–alkenyl (Sections 2.3 and 3) alkynyl–alkenyl (Sections 2.4, 3.2, and 3.3), and alkyl–alkenyl (Sections 2.6, 3.1, and 3.2) couplings that currently appear to be most generally and satisfactorily achieved by the Negishi protocol.

- One of the advantages of the Pd-catalyzed alkenylation by the Negishi coupling is that Al, Zr, and Zn collectively offer various selective hydrometallation and carbometallation reactions, the products of which can be directly used for cross-coupling with minimal synthetic manipulations (Section 3.1).
- The previously underdeveloped and capricious stepwise disubstitution of 1,1-dihalo-1-alkenes has now been developed into a selective, predictable, and satisfactory synthetic method (Section 3.2). The use of organozincs in conjunction with $Pd(DPEphos)Cl_2$ and $Pd(dppf)Cl_2$ in the first substitution step and $Pd[(t\text{-}Bu)_3P]_2$ and related alkylphosphine-containing complexes in the second substitution step has been the key to recent successes in many cases. In the second substitution step of 2-halo-1,3-dienes, the use of $Pd(DPEphos)Cl_2$ and other conventional catalysts containing dppf, PPh_3, and so on has led to potentially useful and near-complete stereoinversion of the carbon–carbon double bond.[163]
- The Pd-catalyzed alkenylation discussed above has been significantly supplemented by the introduction of 1,2-dihaloethylenes and 1-halo-1-buten-3-ynes as two- and four-carbon synthons (Section 3.3). The combined use of 1-halo-1-buten-3-ynes and hydrometallation or carbometallation permits efficient and selective iterative syntheses of oligoenes including oligoene macrolides and carotenoids (e.g., Scheme 20).

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About the Authors

Ei-ichi Negishi, H. C. Brown Distinguished Professor of Chemistry, Purdue University, grew up in Japan and received his Bachelor's degree from the University of Tokyo (1958). He then joined the chemical company Teijin. In 1960, he came to the University of Pennsylvania on a Fulbright Scholarship and obtained his Ph.D. degree in 1963. He then returned to Teijin, and, in 1966, joined Professor H. C. Brown's group at Purdue as a postdoctoral associate. He was appointed Assistant to Professor Brown in 1968. It was during the following few years that he began to see the need for catalytic ways of promoting organoborane reactions. In 1972, he was appointed Assistant Professor in the Department of Chemistry at Syracuse University, where he began his lifelong investigations of transition-metal-catalyzed organometallic reactions for organic synthesis. Between 1976 and 1978, he published about 10 papers describing the Pd- or Ni-catalyzed cross-coupling reactions of various organometals including those of Mg, Zn, B, Al, Sn, and Zr. Today, those cross-coupling reactions that employ organometals containing Zn, Al, and Zr are widely known as the Negishi coupling. Negishi was promoted to Associate Professor at Syracuse University in 1976, and invited back to Purdue University as Full Professor in 1979. In 1999, he was appointed the inaugural H. C. Brown Distinguished Professor of Chemistry. He has received a number of awards, including the 1987 Guggenheim Fellowship, the 1996 A. R. Day Award, a 1997 Chemical Society of Japan Award, the 1998 ACS Organometallic Chemistry Award, a Humboldt Senior Researcher Award, Germany (1998–2001), and the 2000 RSC Sir E. Frankland

Prize Lectureship. At Purdue University, he was the recipient of the 1998 McCoy Award and the 2003 Sigma Xi Award.

Qian Hu graduated from Huazhong University of Science and Technology (China) in 2001 with an M.S. degree in applied chemistry. In 2002, she joined Professor Ei-ichi Negishi's group at Purdue University. In fulfilling a part of the requirements for the Ph.D. degree, she is currently conducting research on the total synthesis of natural products and the development of new synthetic methods in the area of transition-metal-catalyzed cross-coupling reactions.

Zhihong Huang was born in 1979 in Hubei Province, P. R. China. He obtained his B.S. degree in 2001 from the Department of Technical Physics at Peking University. Between 2001 and 2003, he was a member of Professor Jean-Luc Montchamp's group at Texas Christian University, where he received his M.S. degree in 2003. He then joined Professor Negishi's group at Purdue University, where he is currently working on the development of new synthetic methods that are based on transition-metal catalysis and in the area of natural product synthesis.

Mingxing Qian earned his Ph.D. degree in industrial catalysis in 2000 from Dalian University of Technology (China). From August 2001 to March 2005, he worked as a postdoctoral fellow at Purdue University, under the guidance of Professor Ei-ichi Negishi, on palladium-catalyzed carbon–carbon-bond-forming reactions and natural product synthesis. He is currently a postdoctoral research associate in Professor F. Gabbai's group at Texas A&M University, where he is carrying out research on the design, synthesis, and application of transition-metal complexes for olefin oligomerization and polymerization.

Guangwei Wang was born in 1976 in Henan Province, P. R. China. He received his B.S. degree from Lanzhou University in 1998. He then worked in Professor Shengming Ma's group until 2003 at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. In 2004, he enrolled at Purdue University to pursue his Ph.D. degree under the direction of Professor E. Negishi. His research interests include the development of new synthetic methods based on transition-metal catalysis and the synthesis of natural products.

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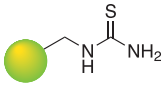
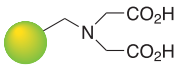
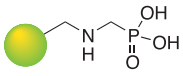
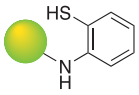
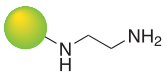
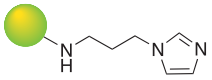
Macroporous Resins

Cat. No.	Name	Structure	Typical Experimental Capacity	Metals Removed	Effective in Acid/Base?
655422	**QuadraPure™ TU** 400–600 µm		0.19 mmol/g (based on $Pd(OAc)_2$ in CH_2Cl_2)	Pd, Pt, Ru, Au, Ag, Cu, Ni, Zn, Hg, Pb, and Cd	Y/Y
657026	**QuadraPure™ IDA** 350–750 µm		0.16 mmol/g (based on $Cu(acac)_2$ in CH_2Cl_2)	Fe, Al, Ga, In, Cu, V, Pb, Ni, Zn, Cd, Be, Mn, Ca, Mg, Sr, and Ba	Y[a]/Y
657611	**QuadraPure™ AMPA** 350–750 µm		0.17 mmol/g (based on $Ni(acac)_2$ in CH_2Cl_2)	Fe, Cu, Ni, Pb, V, Al, Sn, Zn, Cd, Co, Pd, Ca, Mg, Sr, and Ba	Y[a]/Y

[a] pH < 2 gives poor scavenging.

Microporous Resins

They possess excellent scavenging properties, particularly for palladium, at different pH values, and in the presence of competing ligands and substrates. The metal loading capacity can be significantly higher for these microporous products.

Cat. No.	Name	Structure	Functional Group Loading	Metals Removed	Effective in Acid/Base?
657662	**QuadraPure™ MPA** 100–400 µm		1.5 mmol/g	Pd, Ru, Rh, Hg, Au, Ag, Cu, Pb, Ir, Pt, Cd, Co, and Sn	Y/Y
657646	**QuadraPure™ AEA** 100–400 µm		1.3 mmol/g	Pd, Sn, Ru, Pt, Ni, Cu, Zn, and Co	N/Y
657654	**QuadraPure™ IMDAZ** 100–400 µm		1.5 mmol/g	Ni, Pd, Os, Rh, Co, V, Fe, Cu, and Sn	N/Y

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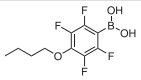
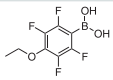


2 g
10 g

4-Ethoxy-2,3,5,6-tetrafluorophenylboronic acid

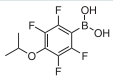
657298
$C_8H_7BF_4O_3$



2 g
10 g

4-Isopropoxy-2,3,5,6-tetrafluorophenylboronic acid

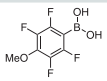
657263
$C_9H_9BF_4O_3$



2 g
10 g

4-Methoxy-2,3,5,6-tetrafluorophenylboronic acid

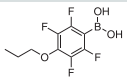
657301
$C_7H_5BF_4O_3$



2 g
10 g

4-Propoxy-2,3,5,6-tetrafluorophenylboronic acid

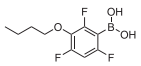
657271
$C_9H_9BF_4O_3$



2 g
10 g

3-Butoxy-2,4,6-trifluorophenylboronic acid

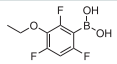
657352
$C_{10}H_{12}BF_3O_3$



1 g
5 g

3-Ethoxy-2,4,6-trifluorophenylboronic acid

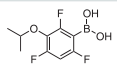
657247
$C_8H_8BF_3O_3$



1 g
5 g

3-Isopropoxy-2,4,6-trifluorophenylboronic acid

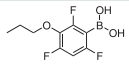
657360
$C_9H_{10}BF_3O_3$



1 g
5 g

3-Propoxy-2,4,6-trifluorophenylboronic acid

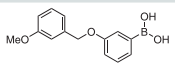
657379
$C_9H_{10}BF_3O_3$



1 g
5 g

3-(3′-Methoxybenzyloxy)phenylboronic acid

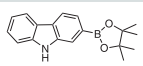
657395
$C_{14}H_{15}BO_4$



2 g
10 g

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole, 90%

655724
$C_{18}H_{20}BNO_2$

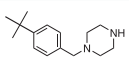


1 g
5 g

Heterocyclic Building Blocks

1-(4-*tert*-Butylbenzyl)piperazine 97%

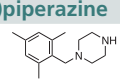
650129
$C_{15}H_{24}N_2$



1 g
5 g

1-(2,4,6-Trimethylbenzyl)piperazine

651680
$C_{14}H_{22}N_2$



1 g
5 g

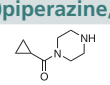
1-(Ethanesulfonyl)piperazine, 97%

653306
$C_6H_{14}N_2O_2S$

1 g
5 g

1-(Cyclopropanecarbonyl)piperazine, 97%

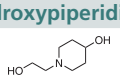
653314
$C_8H_{14}N_2O$



1 g
5 g

1-(2-Hydroxyethyl)-4-hydroxypiperidine, 96%

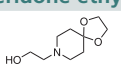
655732
$C_7H_{15}NO_2$



1 g
5 g

1-(2-Hydroxyethyl)-4-piperidone ethylene ketal, 97%

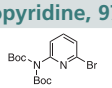
655775
$C_9H_{17}NO_3$



1 g
5 g

6-(Di-Boc-amino)-2-bromopyridine, 97%

655848
$C_{15}H_{21}BrN_2O_2$



5 g
25 g

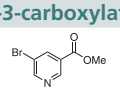
Lithium 3-fluoropyridine-2-carboxylate, 90%

656348
$C_6H_3LiFNO_2$

1 g
5 g

Methyl 5-bromopyridine-3-carboxylate, 97%

657425
$C_7H_6BrNO_2$



5 g

2,6-Dimethoxypyridine-3-carboxaldehyde

657468
$C_8H_9NO_3$

1 g
5 g

2-Acetyl-4-methylthiazole, 97%

656313
C_6H_7NOS

1 g
5 g

6-Isopropyl-1*H*-indole

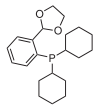
655341
$C_{11}H_{13}N$

1 g
5 g

Organic Reagents and Building Blocks

2-(2′-Dicyclohexylphosphinophenyl)-1,3-dioxolane, 97%

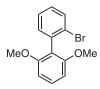
655406
$C_{21}H_{31}O_2P$



1 g

2′-Bromo-2,6-dimethoxybiphenyl, 97%

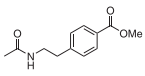
655481
$C_{14}H_{13}BrO_2$



5 g

Methyl 4-(*N*-acetyl-2-aminoethyl)benzoate

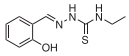
656127
$C_{12}H_{15}NO_3$



5 g

2-Hydroxybenzaldehyde *N*-ethylthiosemicarbazone, 97%

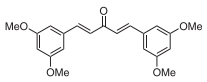
657956
$C_{10}H_{13}N_3OS$



1 g
10 g

(1*E*,4*E*)-1,5-Bis(3,5-dimethoxyphenyl)-1,4-pentadien-3-one, 97%

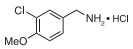
656852
$C_{21}H_{22}O_5$



1 g
5 g

3-Chloro-4-methoxybenzylamine hydrochloride

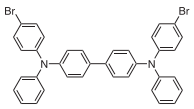
657441
$C_8H_{11}Cl_2NO$



5 g

4,4′-Bis[(4-bromophenyl)phenylamino)]biphenyl

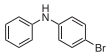
656674
$C_{36}H_{26}Br_2N_2$



1 g

4-Bromodiphenylamine, 97%

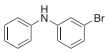
657158
$C_{12}H_{10}BrN$



1 g
5 g

N-(3-Bromophenyl)aniline, 97%

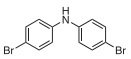
654248
$C_{12}H_{10}BrN$



1 g
10 g

Bis(4-bromophenyl)amine

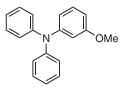
657131
$C_{12}H_9Br_2N$



5 g
25 g

3-Methoxytriphenylamine, 97%

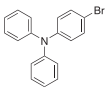
640549
$C_{19}H_{17}NO$



1 g
5 g

4-Bromo-*N*,*N*-diphenylaniline, 97%

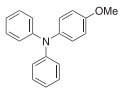
643831
$C_{18}H_{14}BrN$



5 g
25 g

4-Methoxy-*N*,*N*-diphenylaniline, 97%

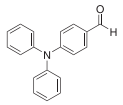
646121
$C_{19}H_{17}NO$



1 g
10 g

4-(Diphenylamino)benzaldehyde, 97%

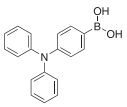
647209
$C_{19}H_{15}NO$



1 g
5 g

4-(Diphenylamino)phenylboronic acid

647292
$C_{18}H_{16}BNO_2$



1 g
5 g

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Ethyl acetate, ≥99.7%	**34972**	1 L, 2.5 L
Methanol, ≥99.9%	**34966**	1 L, 6×1 L, 2.5 L, 4×2.5 L
2-Propanol, ≥99.9%	**34965**	1 L, 6×1 L, 2.5 L, 4×2.5 L
Water	**39253**	1 L

HPLC Grade Solvents	Cat. No.	Pack Size
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Ethyl acetate, 99.9%	**650528**	1 L, 6×1 L, 4 L, 4×4 L
Methanol, ≥99.9%	**646377**	1 L, 4 L, 4×4 L
2-Propanol, 99.9%	**650447**	1 L, 6×1 L, 4 L, 4×4 L
Water	**34877**	1 L, 4 L, 4×4 L

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Enantiopure Sulfoxides and Sulfinamides: Recent Developments in Their Stereoselective Synthesis and Applications to Asymmetric Synthesis


Dr. Chris H. Senanayake


Dr. Dhileepkumar Krishnamurthy


Dr. Zhi-Hui Lu


Dr. Zhengxu Han


Dr. Isabelle Gallou

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Outline

1. Introduction

In recent years, several new methodologies for the asymmetric synthesis of enantiopure sulfoxides and sulfinamides have emerged. The incentive for such prolific research lies in the numerous synthetic applications of these functional groups. Chiral sulfinamides have proven highly efficient as chiral auxiliaries in the synthesis of chiral amines[1] and as ligands in catalytic asymmetric reactions.[2] Chiral sulfoxides, themselves a target functionality in biologically active compounds,[3] have also been widely utilized as

chiral auxiliaries for asymmetric C–C-bond formation,[4] as ligands in catalytic asymmetric processes,[5] and in molecular recognition studies.[6] Despite numerous reports on the preparation of sulfinamides and sulfoxides, a general, practical, and economical approach to these valuable functionalities was still lacking until recently. The present review highlights the latest developments in the synthesis and application of sulfoxides and sulfinamides.

2. Asymmetric Synthesis of Chiral Sulfoxides and Sulfinamides

2.1. Background

The wide variety of methods for preparing optically active sulfoxides belong to either of two distinct approaches: asymmetric oxidation of prochiral sulfides[7] and organometallic addition to electrophilic sulfoxides with inversion of configuration at the sulfur atom.[8] This review will focus on recent advances in the latter approach.[9] The synthesis of unsymmetrical sulfoxides was originally carried out by Gilman in 1926.[10] In 1962, Andersen reported the first chiral sulfinyl transfer agent, (*S*)-menthyl *p*-toluenesulfinate (**1a**), which was used to prepare sulfoxides by addition of organometallics to the S–O bond of **1a** in high yield and excellent enantioselection, albeit with a limited scope.[11] The Andersen method was extended to other chiral alcohols[12] such as **1b**.[13] Khiar, Fernández, Alcudia, and co-workers developed an elegant preparation of optically active sulfoxides and sulfinamides from racemic aryl or alkyl sulfinyl chlorides using diacetone D-glucose as a chiral controller.[13] In 1972, Wudl and Lee disclosed the first cyclic sulfinyl transfer agent, an (–)-ephedrine-derived 1,2,3-oxathiazolidine-2-oxide (**2**), which was utilized to prepare methyl aryl sulfoxides.[14] Later, Hiroi employed the same type of technology using a chiral benzoxathiazine derivative that produced optically active sulfoxides.[15] However, sulfoxides obtained from ephedrine-based oxathiazolidines had low enantioselectivities and yields.[14,15] Use of trimethylaluminum as an additive was required to cleave the unactivated S–N bond and to produce sulfoxides in good yields and high enantioselectivities, except for hindered sulfoxides, such as *tert*-butyl sulfoxides.[16] To overcome these difficulties, Kagan introduced cyclic sulfite **3**, which led to a mixture of regioisomeric sulfinate esters upon treatment with a variety of organometallic compounds.[17] Treatment of the purified sulfinate esters with a second organometallic agent produced chiral sulfoxides in excellent enantioselectivities and good yields (**Figure 1**).

Evans's *N*-sulfinyloxazolidinone **4** and, more recently, Oppolzer's *N*-sulfinylsultam **5** produced chiral sulfoxides in high enantioselectivities;[18,19] but these chiral sulfinyl transfer agents were mostly limited to the preparation of aryl sulfoxides. Later on, Ellman synthesized the optically pure *tert*-butyl *tert*-butanethiosulfinate (**6**) and utilized it for the production of a variety of *tert*-butyl sulfoxides in excellent enantioselectivities and high yields.[20] A number of other methodologies for the preparation of optically active sulfoxides have also emerged, but they still lack generality.[21] Recently, Senanayake and co-workers introduced the N-activated 1,2,3-oxathiazolidine-2-oxide derivatives **7**, which enabled the highly general, selective, and practical synthesis of a wide range of chiral sulfoxides and sulfinamides in high yields and excellent enantioselectivities (**Scheme 1**).[22] The key to the success of this new technology resides in the utilization of readily available activated amino alcohols and thionyl chloride to build the novel and reactive sulfinyl transfer agents **7**.

2.2. Preparation of Sulfoxides

Three decades ago, Wudl and Lee demonstrated the utility of (–)-ephedrine-derived 1,2,3-oxathiazolidine-2-oxide **2** for the enantioselective synthesis of chiral sulfoxides. When **2** was subjected to carbon nucleophiles, the reactive S–O bond was cleaved selectively and produced *N*-methylsulfinamides. Addition of a second carbon nucleophile displaced the S–N bond of these acyclic sulfinamides and led to optically active sulfoxides. However, this second displacement resulted in poor enantioselectivities and yields (**Scheme 2**).[14]

Senanayake and co-workers reasoned that electron-donating groups, such as methyl, on the nitrogen of the oxathiazolidine oxide would strengthen the S–N bond, while weakening the S–O bond of **2**.[23] Thus, substituting an electron-withdrawing group for the methyl group on the nitrogen should act as an activator and reverse the bond strengths and order of bond cleavage (S–N before S–O) (**Figure 2**).[22a]

To test this hypothesis, Senanayake's group chose to utilize an arylsulfonyl group as a nitrogen-activating group and the indan platform as the conformationally constrained backbone. Synthetic investigations aimed at preparing the required 1,2,3-oxathiazolidine-2-oxide starting materials indicated that the base–solvent combination used in the reaction of aminoindanol **12** with $SOCl_2$ had a pronounced effect on the endo/exo ratio of the product, **13** (**eq 1**).[22b] After extensive base screening, it was determined that using Ar = 2,4,6-mesityl and 3,5-lutidine as base in THF gave the best endo/exo selectivity of 97:3. The high endo selectivity was switched to a high exo selectivity by a simple change in the pyridine substitution pattern. Thus, using sterically congested 2,6-di-*tert*-butylpyridine led to 2:98 (Ar = 4-tolyl) and 7:93 (Ar = 2,4,6-mesityl) endo/exo selectivities. After recrystallization, both endo and exo isomers of **13** were prepared in kilogram quantities from one enantiomer of the indan platform in diastereomerically and enantiomerically pure forms.

To illustrate the power of this approach, treatment of either *endo*- or *exo*-**13a** (Ar = 2,4,6-mesityl) with *tert*-butylmagnesium chloride at low temperature led to the chemoselective cleavage of the S–N bond in each to produce the corresponding diastereomers of sulfinate **14** in >90% yields and with inversion of configuration at the sulfur atom (**Scheme 3**).[22b] Upon treatment with *i*-PrMgCl, the individual diastereomeric sulfinate, **14**, provided the corresponding enantiomer of *tert*-butyl isopropyl sulfoxide (**15**)—with inversion of configuration at the sulfur atom—in excellent yield and with outstanding recovery of enantiopure **12a** (>96%).

Other *N*-sulfonylamino alcohols were also evaluated as oxathiazolidine oxide precursors. Inexpensive and readily available *N*-toluenesulfonylnorephedrine, (*R,S*)-**16**, was found to be an ideal template for the preparation of *N*-toluenesulfonyl-4-methyl-5-phenyl-1,2,3-oxathiazolidine-2-oxide (TMPOO, **17**). Similarly to **13**, oxathiazolidine oxide **17** was subjected to successive nucleophilic attacks on the sulfur atom in order to evaluate the scope of the methodology (**Scheme 4**).[22b] It was discovered that the S–N bond of TMPOO could also be cleaved with mild reagents such as organozincs of sterically congested halides to give the sulfinate intermediates. In addition to alkyl–alkyl chiral sulfoxides, this powerful process gave access to either enantiomer of alkyl–aryl and aryl–aryl sulfoxides. Finally, *tert*-butyl (*tert*-butanesulfinyl)acetate and diethyl (*tert*-butanesulfinyl)methylphosphonate were generated by addition of the appropriate lithium reagent to the corresponding *tert*-butanesulfinate, which demonstrated the ability of this methodology to access a variety of novel structures and possibly lead to new biological targets.[22b]

2.3. Preparation of Sulfinamides

Pioneering work by Davis and co-workers underlined the importance and utility of enantiomerically pure sulfinamides as

building blocks in the asymmetric synthesis of amine derivatives.[1] Davis's *p*-toluenesulfinamide (**19**), prepared from Andersen's menthyl ester **1a**, was condensed with aldehydes and ketones to produce chiral sulfinyl imines (**Scheme 5**).[24] The sulfinyl group not only stabilized imines, but also activated them toward addition of a wide range of nucleophiles. Furthermore, the chiral substituent on the imine nitrogen provided high diastereofacial selectivity for nucleophilic addition on the imine carbon, leading to chiral sulfinamides **21**. The sulfinyl group was readily cleaved by brief treatment with acid, thus providing a very general approach for the asymmetric synthesis of a broad range of amine-containing compounds.[1,2,24]

Ellman and co-workers later demonstrated the overall differences between the *tert*-butanesulfinyl and the *p*-toluenesulfinyl groups. Interestingly, *tert*-butanesulfinamide proved more nucleophilic than *p*-toluenesulfinamide in the direct condensation with aldehydes and ketones. It was also more stereo- and regioselective upon nucleophilic attack, because of the greater steric hindrance and electron-donating properties of the *tert*-butyl as compared to those of the *p*-tolyl group.[25]

The asymmetric oxidation of di-*tert*-butyl disulfide (**22**), using hydrogen peroxide with $VO(acac)_2$ and ligand **23**, proceeded in high yield and enantioselectivity. Displacement of *tert*-butylthiolate from intermediate **24** with lithium amide provided *tert*-butanesulfinamide (**25**) in an analytically and enantiomerically pure form by crystallization (**Scheme 6**).[25] Application of this method to the preparation of other sulfinamides has not been reported.

Senanayake and co-workers extended their strategy for the preparation of chiral sulfoxides to the synthesis of *tert*-butanesulfinamide. Reaction of (1*R*,2*S*,*R*)-**14** or (1*R*,2*S*,*S*)-**14** with Li/NH_3/THF at –78 °C led to cleavage of the S–O bond with inversion of configuration at the sulfur atom, and gave rise to the corresponding enantiomers of *tert*-butanesulfinamide in quantitative yields. When the inexpensive oxathiazolidine oxide **17** was reacted first with *t*-BuMgBr and then with lithium amide, (*S*)-*tert*-butanesulfinamide was formed in 89% yield and 99% ee. A wide variety of structurally diverse tertiary alkyl and aryl sulfinamides were obtained with this double-inversion nucleophilic displacement strategy (**Scheme 7**).[23a]

Recently, Ellman and co-workers developed the first and unique multistep synthesis of a support-bound *tert*-butanesulfinamide derivative from enantiopure sulfinamide precursor (*S*)-**26g**.[26] However, the synthesis of (*S*)-**26g** required reduction of the benzylic position of a derivative of the chiral auxiliary (*S*)-2-amino-1,1,2-triphenylethanol. Thus, the expensive (*S*)-2-amino-1,1,2-triphenylethanol could not be recovered.[26] Using our approach, (*S*)-**26g** was prepared efficiently in excellent yield and optically pure form with efficient recovery of auxiliary (1*R,2S*)-**16**. The synthesis of a novel benzyl ether derived sulfinamide, (*S*)-**26h**, was also demonstrated. Sulfinamide (*S*)-**26h** and other ether-functionalized sulfinamides are potential precursors of ether-tethered, support-bound *tert*-butanesulfinamides.[27] This methodology has provided the first *modular* synthesis of this valuable family of enantiopure sulfinamides.

3. Chiral Sulfinyl Auxiliaries in Asymmetric Synthesis

Sulfinamides can be condensed with aldehydes and ketones to form *N*-sulfinyl imines in good yields. Nucleophilic addition followed by cleavage of the sulfinyl group leads to chiral primary amines. Davis and Ellman have used this method extensively to produce a variety of chiral amines using *p*-toluene- and *tert*-butanesulfinamides.[24,25] Recently, Ellman reported the highly diastereoselective

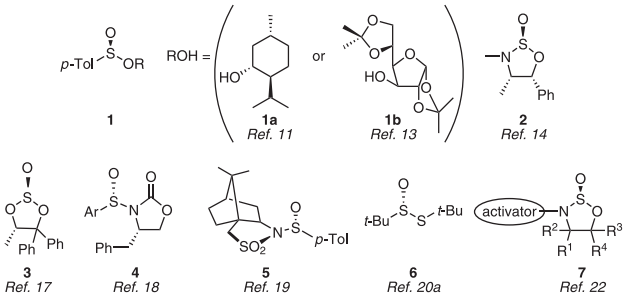
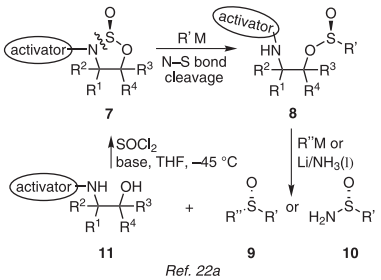
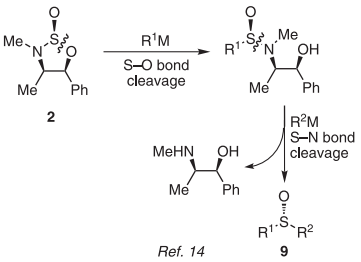


Figure 1. Selected Chiral Sulfinyl Transfer Agents.



Scheme 1. N-Activated Oxathiazolidine-2-oxides as Precursors of Chiral Sulfoxides and Sulfinamides.



Scheme 2. Wudl and Lee's Synthesis of Chiral Sulfoxides.

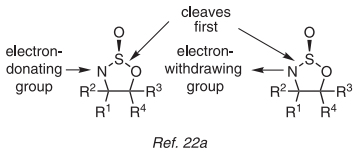
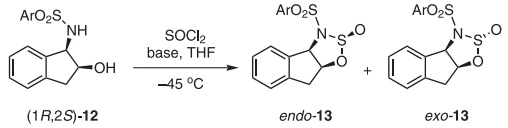


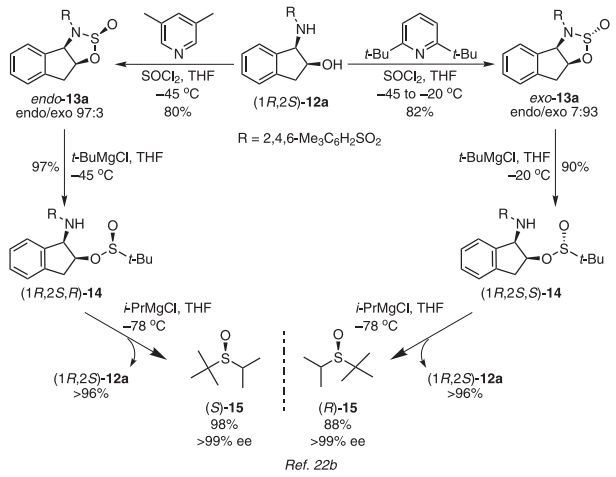
Figure 2. Activation Strategy for Oxathiazolidine Oxides.



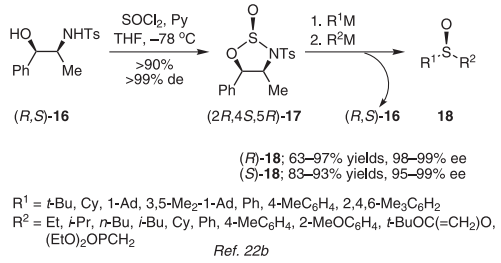
SM	Ar	Base	13 Yield	13 Endo/Exo
12a	2,4,6-mesityl	3,5-lutidine	80%	97:03
12a	2,4,6-mesityl	2,6-di-*t*-butylpyridine	82%	07:93
12b	4-tolyl	2,6-di-*t*-butylpyridine	85%	02:98

Ref. 22b

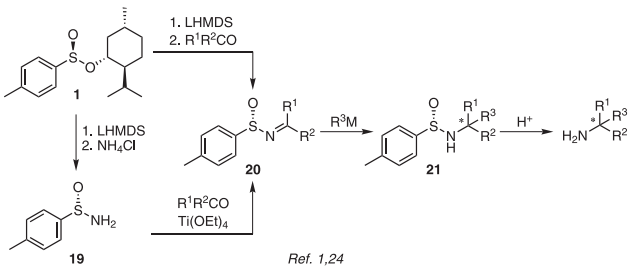
eq 1



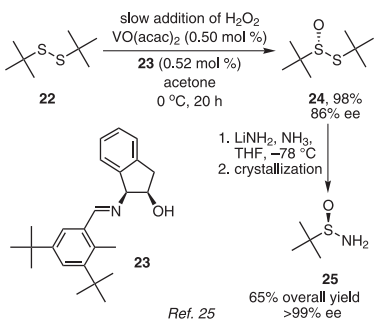
Scheme 3. Synthesis of Enantiomerically Pure (*R*)- and (*S*)-*tert*-Butyl Isopropyl Sulfoxides.



Scheme 4. Modular Asymmetric Synthesis of Enantiopure Sulfoxides.



Scheme 5. Asymmetric Synthesis and Reactions of *p*-Toluenesulfinyl Imines.



Scheme 6. Asymmetric Synthesis of *tert*-Butanesulfinamide.

addition of alkyl or aryl Grignard reagents to *N*-sulfinyl imines, **27**, derived from 3- and 4-substituted cyclohexanones (**eq 2**).[28] The reaction proceeded in good yields, but the selectivity appeared to be controlled by the cyclohexane ring substituents rather than the sulfinyl group stereochemistry. Therefore, *racemic tert*-butanesulfinamide was employed. Cleavage of the sulfinyl group in **28** provided α-substituted cyclohexylamines, a prevalent substructure in drugs and drug candidates.[28]

3.1. Synthesis of 1,2-Diamines

A novel, straightforward, and highly efficient synthesis of C_2-symmetrical vicinal diamines was developed very recently by Xu and co-workers (**Scheme 8**).[29] The homocoupling reaction of a variety of *N*-sulfinyl aldimines, **29**, proceeded smoothly using 2 equivalents of SmI_2 and 2 to 6 equivalents of HMPA in THF at –78 °C and produced the *d/l*-adducts, **30**, as single stereoisomers in moderate-to-high yields. Amine deprotection led to enantiopure C_2-symmetrical vicinal diamines, **31**. Davis and Deng reported an efficient asymmetric synthesis of both *syn*- and *anti*-α,β-diamino esters with high diastereoselectivities and good yields by addition of differentially N-protected glycine enolates to enantiopure sulfinyl imines and subsequent deprotection.[30]

3.2. Synthesis of Amino Alcohols

Senanayake and co-workers developed an efficient method for accessing *syn*- and *anti*-1,2-amino alcohols, as exemplified by the synthesis of *syn*-(3*R*,4*R*)-**35** and *anti*-(3*S*,4*R*)-**35** from a common *tert*-butanesulfinyl imine starting material, (*S*)-**32** (**Scheme 9**).[31] Good-to-excellent yields and high diastereoselectivities (>98%) were observed for the protected amino alcohol intermediates, **34**. Deprotection with HCl in methanol produced the corresponding enantiomerically enriched 1,2-amino alcohols in high yields.

A remarkable and general method for the asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols has recently been reported (**Scheme 10**).[32] The first application of metalloenamines derived from *N*-sulfinyl imines was reported for the highly diastereoselective addition to aldehydes. Reduction of the resulting β-hydroxy-*N*-sulfinyl imines, **37**, with catecholborane or $LiBHEt_3$ provided *syn*- and *anti*-1,3-amino alcohols with very high diastereomeric ratios. This method was found to be effective for a variety of imines and aldehydes. The convergent and efficient asymmetric syntheses of two natural products, (–)-8-epihalosaline and (–)-halosaline, were also accomplished.

Although addition of ester enolates to sulfinyl imines to afford β-amino esters has been well studied by Davis's and Ellman's groups, the diastereoselective addition of ketone enolates to *N*-sulfinyl imines has received much less attention. Recently, Davis and Yang reported a practical and elegant solution for the direct and highly diastereoselective asymmetric synthesis of β-amino ketones by addition of potassium enolates of methyl ketones to *N*-sulfinyl imines (**eq 3**).[33] Another very recent example of a highly diastereoselective synthesis of *syn*- and *anti*-1,3-amino alcohols has been reported by Nelson and co-workers.[34]

Senanayake and co-workers recently demonstrated that both enantiomers of 1,4-amino alcohols could be obtained from a single enantiomer of a sulfinyl imine, simply by changing the reaction solvent. Using THF as solvent, the addition of Grignard reagents (*R*)- or (*S*)-**44** to a common sulfinyl imine, (*R*)-**32**, allowed rapid access to the chiral amines with the *R* configuration at the amine carbons. In CH_2Cl_2, on the other hand, the same reactions led to the stereoisomers with the *S* configuration at the amine carbons (**Scheme 11**).[31] The observed reversed diastereoselectivity in CH_2Cl_2 and THF implies that the reaction may be taking place

through a chelated cyclic transition state in CH_2Cl_2 and a nonchelated acyclic transition state in THF. It has been postulated that different aggregation states of Grignard reagents in CH_2Cl_2 and THF might have an influence on the rate of the reaction.[31]

3.3. Synthesis of α-Amino Ketones

N-Sulfinyl-α-amino-1,3-dithioketals have recently been prepared in high de's and good yields by treating sulfinyl imines with lithio-1,3-dithianes. Selective removal of the *N*-sulfinyl or the thioketal groups affords stable α-amino-1,3-dithioketals or *N*-sulfinyl-α-amino ketones, respectively (**Scheme 12**).[35]

3.4. Synthesis of Amino Acids

The preparation of α-amino acids by asymmetric addition of cyanide to sulfinyl imines has been well documented by both Davis's and Ellman's groups.[36] Recently, Hou and co-workers described the reaction of chiral sulfinimines, derived from aliphatic aldehydes, with TMSCN in the presence of CsF under mild conditions. This CsF-promoted addition complements Davis's protocol. The addition gave α-amino nitriles with high diastereoselectivities (up to 98% de) and yields (92–99%) (**Scheme 13**).[36a] The formation of an intermediate *N*-sulfinyl enamine was suggested to play a crucial role in this TMSCN addition reaction. α,β-Diamino acid derivatives were also obtained in high diastereoselectivities (92–96% de) and yields (98%) from a similar reaction of 2-aziridinesulfinimines (R = *N*-benzylaziridin-2-yl) with TMSCN, followed by ring-opening of the aziridine ring in the α-aminonitrile intermediate with thiophenol.

The application of sulfinyl imines in the synthesis of β-amino acids from ester enolates has been well investigated independently by Davis, Ellman, and Adamczyk.[36b–e] This method is very general and allows access to a variety of β-substituted, α,β- and β,β-disubstituted, as well as α,β,β- and α,α,β-trisubstituted amino acids in high stereoselectivities.

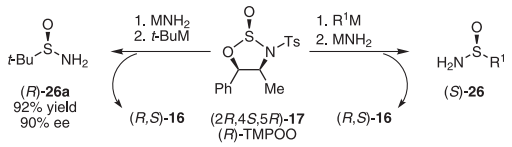
3.5. Synthesis of Aziridines

An efficient method for the preparation of enantiopure *N*-*tert*-butanesulfinyl aziridines was described by Chemla and Ferreira (**eq 4**).[37] Condensation of enantiopure *N*-*tert*-butanesulfinyl imines (R_S)-**49** with racemic allenylzinc bromide **50** afforded *trans*-ethynyl aziridines (R_S)-**51** in good-to-excellent yields and with excellent diastereoselectivities (>98%). The absolute stereochemistry of enantiopure (R_S)-**51** was shown to be (R_S,2*R*,3*R*) and to result from a chelation-type transition state in which the zinc atom of allenylzinc **50** coordinated both the nitrogen and the oxygen atoms of the sulfinyl imine. Removal of the *N*-*tert*-butanesulfinyl auxiliary of aziridines (R_S)-**51** by treatment with HCl in MeOH, led to the corresponding enantiomerically pure deprotected aziridines.[37]

Chiral, nonracemic vinyl aziridines have been conveniently prepared via a Darzens-type reaction between sulfinyl imines and α-haloenolates, which gave *cis*-*N*-sulfinylaziridine-2-carboxylates.[38] More recently, Stockman and co-workers reported a straightforward approach to the synthesis of a range of chiral alkyl and aryl vinyl aziridines, in high yields and excellent diastereoselectivities, by reaction of *tert*-butanesulfinyl imines with the ylide derived from *S*-allyltetrahydrothiophenium bromide (**eq 5**).[39]

3.6. Synthesis of α-Amino Phosphonates

Recently, Davis's group reported an asymmetric synthesis of *cis*-5-substituted pyrrolidine-2-phosphonates, which serve as proline surrogates (**Scheme 14**).[40] δ-Amino-α-diazo-β-ketophosphonates were synthesized from the corresponding *N*-sulfinyl-β-amino esters in five steps. Subsequent intramolecular metal carbenoid

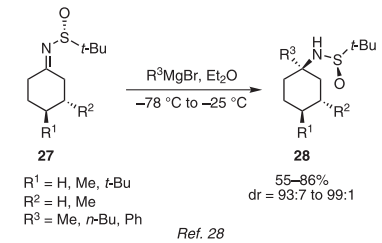


26	R^1	(*S*)-26 Yield[a]
a	*t*-Bu	89%
b	$EtMe_2C$	90%
c	Et_3C	87%
d	4-MeC_6H_4	83%
e	2,4,6-$Me_3C_6H_2$	80%
f	1-Ad	80%
g	$(CH_2{=}CHCH_2CH_2)Me_2C$	90%
h	$(BnOCH_2CH_2)Me_2C$	85%

[a] 99% ee in all cases, except for (*S*)-**26h**.

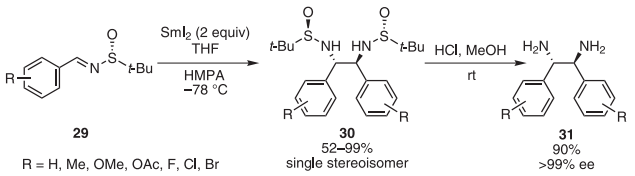
Ref. 23a

Scheme 7. Modular Asymmetric Synthesis of Enantiopure Sulfinamides by Double-Inversion Nucleophilic Displacement.



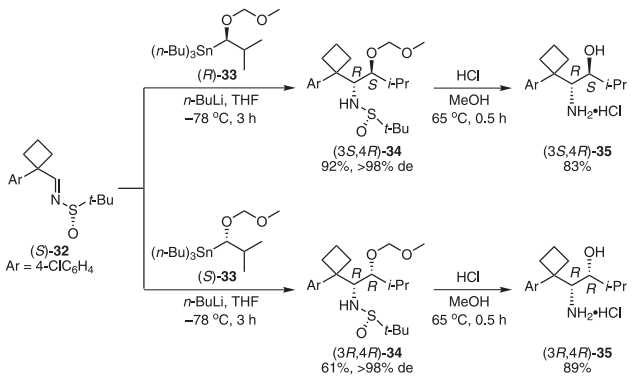
Ref. 28

eq 2



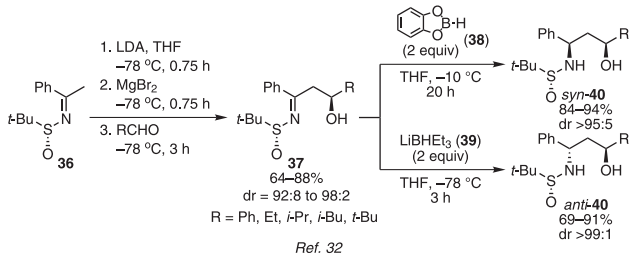
Ref. 29

Scheme 8. Chiral Sulfinyl Auxiliaries in the Asymmetric Synthesis of C_2-Symmetrical Vicinal Diamines.

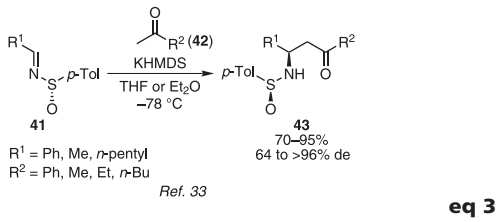


Ref. 31

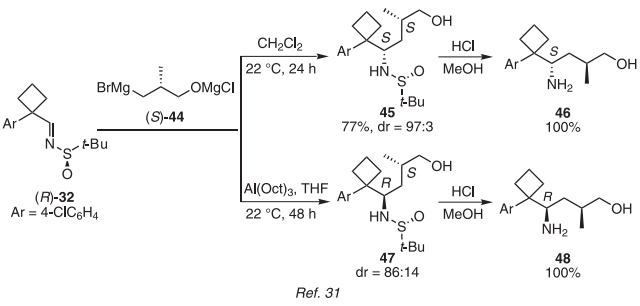
Scheme 9. Asymmetric Synthesis of *syn*- and *anti*-1,2-Amino Alcohols.



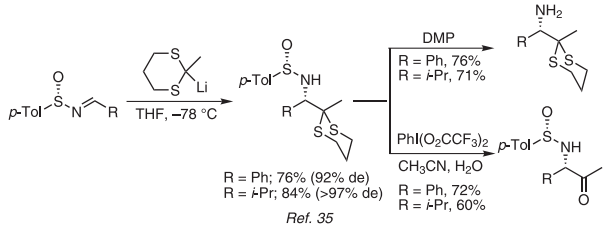
Scheme 10. Ellman's Asymmetric Synthesis of *syn*- and *anti*-1,3-Amino Alcohols.



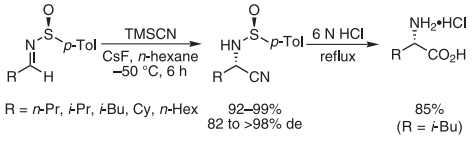
eq 3



Scheme 11. Asymmetric Synthesis of 1,4-Amino Alcohols.



Scheme 12. Asymmetric Synthesis of α-Amino Ketones.



Scheme 13. Asymmetric Synthesis of α-Amino Acids.

N–H insertion led to cis 3-oxopyrrolidinephosphonates in 62–98% de's. Removal of the 3-oxo group led to cis, 5-substituted pyrrolidinephosphonates.

The same group also developed an alternative approach for preparing five-, six-, and seven-membered cyclic α-amino phosphonates, in enantiomerically pure form, via the highly diastereoselective addition of metal phosphonates to masked oxosulfinyl imines. Hydrolysis of the resulting masked oxo-α-amino phosphonates, followed by reduction of the intermediate cyclic imino phosphonates, afforded the cyclic α-amino phosphonates in good overall yields.[41]

3.7. Synthesis of α-Amino Organostannanes

Chiral, nonracemic α-amino organostannanes have been prepared by the highly diastereoselective (de > 98%) addition of Bu_3SnLi to chiral *tert*-butanesulfinyl imines (**Scheme 15**).[42] The resulting adducts were obtained in excellent yields, and were readily converted to enantiomerically enriched *N*-Boc-protected α-amino organostannanes with complete retention of configuration. Kells and Chong also extended this method to the preparation of chiral α-sulfonamido organostannanes to be used in the Stille cross-coupling reaction.[43] Addition of lithium tributylstannane to (*R*)-*tert*-butanesulfinyl imines derived from aryl aldehydes provided α-sulfinamidostannanes with high diastereoselectivities (de > 98%). Subsequent oxidation with *m*-CPBA gave α-sulfonamidostannanes, which were subjected to Pd/Cu-catalyzed Stille-type coupling with benzoyl chloride. Best yields were achieved using the electron-rich tris(2,4,6-trimethoxyphenyl)phosphine as the ligand. Inversion of configuration at the benzylic carbon was observed.[43]

4. Chiral Sulfoxides and Sulfinamides as Ligands in Catalytic Asymmetric Reactions

Chiral sulfoxides and sulfinamides constitute a valuable class of chiral ligands, where chirality resides at sulfur rather than carbon, and where coordination to the metal can occur through nitrogen, sulfur, or oxygen.

4.1. Chiral Sulfoxide-Based Ligands

Chiral sulfoxides have been used in a number of transition-metal-catalyzed asymmetric carbon–carbon-bond-forming reactions and enantioselective protonation reactions.[44,45] For example, Hiroi and co-workers utilized new chiral oxazoline–sulfoxide ligands for the catalytic asymmetric Diels–Alder reaction of cyclopentadiene and *N*-acryloyloxazolidinone (**eq 6**).[46] These results revealed that the presence of a methoxy group in both the naphthylsulfinate substituent and the oxazoline group was crucial to achieving high asymmetric induction (entry 2). Chiral centers in the oxazoline group and at the sulfur atom play a critical role in the asymmetric Diels–Alder reaction, as removal of either one results in poor enantioselectivities.

N-Phosphanopyrrole and indole, substituted at the 2 position with a chiral sulfoxide group, have successfully been utilized by Hiroi's group as new ligands in the enantioselective palladium-catalyzed allylic alkylation reaction.[47]

4.2. Chiral Sulfinamide-Based Ligands

4.2.1. Asymmetric Diels–Alder Reaction

By developing bis(sulfinyl)imidoamidine (SIAM) ligands, Ellman and coworkers made an outstanding contribution to the chiral Lewis acid catalyzed Diels–Alder reaction of cyclic and acyclic dienes with *N*-acryloyloxazolidinones (**eq 7**).[5f,48] Indeed, SIAM ligands proved far more powerful than previously developed sulfinyl-based ligands. For example, the Diels–Alder reaction of cyclopentadiene and *N*-acryloyloxazolidinone in the presence of

10 mol % $Cu(SbF_6)_2$ and 11 mol % **52** provided the cycloadduct in 96% yield, 98% de, and 98% ee. Modification of the substitution pattern in the SIAM ligand resulted in no further improvement in reactivity or selectivity. SIAM ligands derived from *tert*-butanesulfinamide and ketones provided inferior results. The substrate scope of this $Cu(SbF_6)_2$–SIAM catalytic system was investigated with ligand **52**. High selectivities were observed for imides derived from crotonic acid, cinnamic acid, and fumaric acid (entries 2–4). Less reactive dienes such as 1,3-cyclohexadiene led to the cycloadduct in only 50% yield and 90% ee.

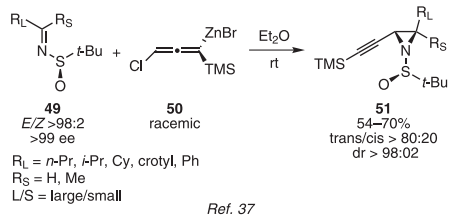
The Cu(II)–SIAM catalytic system proved more efficient than the usual bisoxazoline-based ligand system,[49] even for the more challenging Diels–Alder reaction with acyclic dienes (**eq 8**).[48] Indeed, the use of $Cu(SbF_6)_2$–SIAM catalysts led to high yields and excellent enantioselectivities for the cycloaddition of isoprene and 2,3-dimethylbutadiene. Incorporation of a substituent at the terminal position, or of a phenyl or ether group, in the dienes resulted in poor selectivities. Cycloaddition of 2,3-dimethylbutadiene with substituted dienophiles represented a more challenging set of substrates, and provided disappointing results with ligand **52**. However, using the more reactive *N*-(2,2,2-trifluoroethyl)-substituted SIAM analog of **52** resulted in the formation of the cycloadduct in 80% yield and 81% ee.

4.2.2. Asymmetric Allylic Alkylation

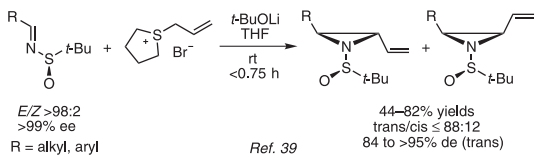
The usefulness of sulfinyl imine ligands in achieving excellent enantioselectivities in the palladium-catalyzed asymmetric allylation reaction has recently been reported by Ellman.[50] An initial optimization study was performed using phosphinooxazoline-based ligand **53a** in the asymmetric alkylation of 1,3-diphenylpropen-1-yl acetate with dimethyl malonate. It was determined that the Pd complex generated from ligand **53a** and a slight excess of $[Pd(allyl)Cl]_2$ (1:1.3) in methylene chloride gave optimal results with high conversion and 93% ee (**eq 9**). Modified ligands (**53b–e**) were prepared and studied in the reaction. Interestingly, using the *p*-toluenesulfinyl ligand **53b** led to poor conversion and no selectivity. Although ketimine ligand **53c** increased the rate of the reaction, a significant reduction in stereoselectivity was also observed. Replacement of phenyl substituents on the phosphorus atom in **53a** by cyclohexyl groups, as in **53d**, gave disappointing results as a longer reaction time was required and poor selectivity was obtained. Interestingly, the Pd complex derived from ligand **53e** was more active and selective and provided 96% ee with complete conversion in 2 hours. Additional experiments showed that ligand **53e** tolerated various ligand/Pd ratios and high-to-low concentrations. More importantly, a lower catalyst loading (5 mol %) provided complete conversion with a 95% isolated yield and 94% ee.

4.2.3. Asymmetric Hydrogenation of Olefins

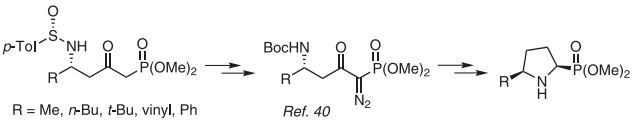
The value of these sulfinamide-based P,N ligands in the asymmetric hydrogenation of olefins has recently been demonstrated (**eq 10**).[51] Initial optimization focused on the hydrogenation of trisubstituted olefin **54a** using iridium complex **55**. The optimal reaction conditions consisted of treating **54a** with 5 mol % of **55** in dichloromethane under 25–100 bars of hydrogen gas pressure, and provided **56a** with >99% conversion and 94% ee. In order to explore the effect of catalyst structure on the turnover and enantioselectivity, an array of similar catalysts with modified sulfinamide moieties or phosphine substituents were prepared. Unfortunately, none was found as effective as **55**. Other functionalized olefins, e.g., **54b**, hydrogenated using catalyst **55**, provided **56b** with >99% conversion and 65% ee. A survey of other catalysts provided only disappointing results. Nonetheless, this work expands the scope of the P,N-sulfinyl imine



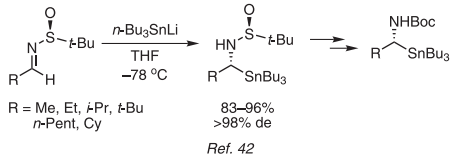
eq 4



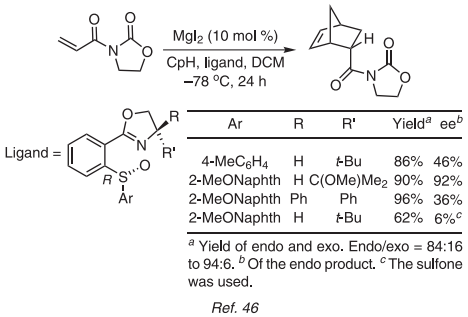
eq 5



Scheme 14. Asymmetric Synthesis of Cis 5-Substituted Pyrrolidine-2-phosphonates.



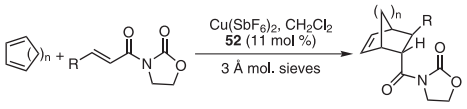
Scheme 15. Asymmetric Synthesis of α-Amino Organostannanes.

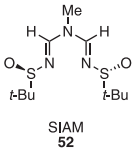


Ar	R	R'	Yield[a]	ee[b]
4-MeC$_6$H$_4$	H	*t*-Bu	86%	46%
2-MeONaphth	H	C(OMe)Me$_2$	90%	92%
2-MeONaphth	Ph	Ph	96%	36%
2-MeONaphth	H	*t*-Bu	62%	6%[c]

[a] Yield of endo and exo. Endo/exo = 84:16 to 94:6. [b] Of the endo product. [c] The sulfone was used.

eq 6





SIAM
52

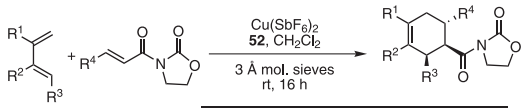
n	R	T, °C	Time	Yield	dr	ee
1	H	–78	0.1 h	96%	99:1	98%
1	Me	–40	8 h	76%	98:2	97%
1	Ph	0	16 h	58%	95:5	94%
1	CO_2Et	–78	2 h	85%	97:3	96%
1	H[a]	–78	8 h	95%	99:1	98%
2	H	0	16 h	50%	98:2	90%

[a] **52** (1 mol %).

SIAM = bis(sulfinyl)imidoamidine

Ref. 48

eq 7

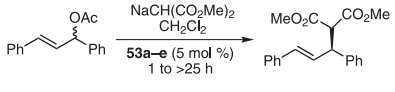


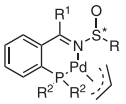
R^1	R^2	R^3	R^4	Yield	ee
Me	H	H	H	83%	93%
Me[a]	Me	H	H	96%	92%
H[b]	H	Me	H	18%	41%
Ph[c]	H	H	H	87%	45%
$CH_2OTBDPS$	H	H	H	33%	62%
Me	Me	H	CO_2Et	<65%	53%

[a] 0 °C. [b] dr of product = 2.0:1.0:0.4; % ee is of major isomer. [c] 2 h.

Ref. 48

eq 8





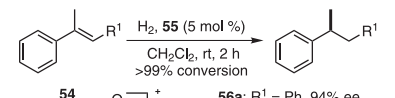
L–Pd
53

Cat.[a]	R	R^1	R^2	ee
53a	*t*-Bu	H	Ph	93%
53b	*p*-Tol	H	Ph	0%
53c	*t*-Bu	Me	Ph	56%
53d	*t*-Bu	H	Cy	49%
53e	*t*-Bu	H	*o*-Tol	96%
53e[b]	*t*-Bu	H	*o*-Tol	96%
53e[c]	*t*-Bu	H	*o*-Tol	94%

[a] **L** (30 mol %),**L–Pd** 1:1.3.
[b] **L–Pd** 1:1.
[c] **L** (5 mol %),**L–Pd** 1:1.

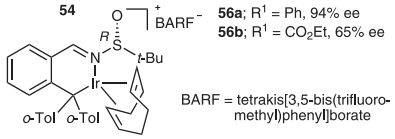
Ref. 50

eq 9



54

56a; R^1 = Ph, 94% ee
56b; R^1 = CO_2Et, 65% ee



BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

55

Ref. 51

eq 10

based catalyst to challenging unfunctionalized olefin substrates and to obtaining valuable structure–activity relationships for sulfinyl imine based ligands in the iridium-catalyzed asymmetric hydrogenation of olefins.

5. Application to the Asymmetric Synthesis of Biologically Active Targets

5.1. Synthesis of SC-53116

SC-53116 is a drug candidate for serotonin 5-HT_4 agonist. Its recent, efficient, and elegant asymmetric synthesis began with the self-condensation of a metalloenamine (derived from *tert*-butylsulfinamide and LiHMDS) in the presence of DMPU in THF, and led to the desired self-condensation product in 55% yield and a good diastereomeric ratio. This compound underwent a novel and selective microwave-assisted decomposition of the *N*-sulfinyl imine moiety to give the corresponding nitrile in 84% yield (**Scheme 16**).[52] Elaboration of the nitrile provided SC-53116 in 29% overall yield (5 steps), a significant improvement over the previously reported synthesis.

5.2. Total Synthesis of (6R,7S)-7-Amino-7,8-dihydro-α-bisabolene

(6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene is an antimicrobial metabolite**.** Its first asymmetric total synthesis utilized a single chiral sulfinyl imine to control the formation of two adjacent stereocenters (**Scheme 17**).[53] The key step, allylation of amidine **57**, was performed at –78 °C with allyl bromide in the presence of KHMDS to provide **58** in 82% yield as a single diastereomer. *N*-Sulfinylamidine **57** was used, because of the increased nucleophilicity of the corresponding metalloenamine towards alkyl halides, as compared to that of metalloenamines derived from *N*-sulfinyl ketimines. The desired ketimine **59** was prepared in 82% yield using a $CeCl_3$-mediated addition of MeLi to amidine **58**. Subsequent ring-closing metathesis of **59** proceeded in 87% yield using a Grubbs second-generation catalyst. This organometallic addition to *N*-sulfinyl ketimines provides the only general method to date for the asymmetric synthesis of tertiary carbinamines. Finally, precomplexation of imine **60** with Me_3Al at –78 °C, followed by addition of 4-methyl-3-penten-1-yllithium and deprotection with HCl in MeOH, led to the natural product, **61**, in 49% yield as a single diastereoisomer.

5.3. Asymmetric Synthesis of (–)-Pateamine

(–)-Pateamine (**65**), a unique thiazole-containing 19-membered bislactone that is isolated from a marine sponge, exhibits potent immunosuppressant activity. Its synthesis has been described by Remuiñán and Pattenden, and involves the asymmetric addition of a functionalized enolate, derived from **62**, to *N*-sulfinyl imine **63** (**Scheme 18**).[54] The resulting β-amino ester, **64**, was isolated in 63% yield and 85% diastereomeric excess. Further synthetic manipulations led to the natural product. Davis and co-workers have also employed this approach in concise and convergent asymmetric syntheses of other biologically active compounds.[55]

5.4. Synthesis of Polyoxamic Acid Lactone

The sulfinyl imine based asymmetric Strecker reaction represents one of the most efficient and practical methods for the synthesis of optically active α-amino acids. Polyoxamic acid, the key structural unit in the natural product polyoxin J, was recently synthesized in an asymmetric fashion starting with the addition of Et_2AlCN to a functionalized *p*-toluenesulfinyl imine. Subsequent deprotection and cyclization of the α-(sulfinylamino)nitrile led to polyoxamic acid lactone (**Scheme 19**).[55]

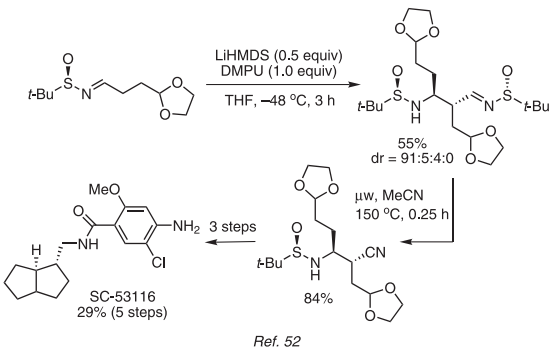
5.5. Synthesis of Single Enantiomers of Sibutramine and Cetirizine

The first application of tunable alkyl or aryl sulfinamides was recently reported for the asymmetric synthesis of **67**, a key intermediate of enantiopure sibutramine. The racemic form of sibutramine is currently used for the treatment of obesity. Among the variety of sulfinamides examined, *tert*-butanesulfinamide and (triethyl)methanesulfinamide (TESA) provided the best yields and selectivities for this process. After further optimization with respect to temperature, additives, and solvent, it was determined that using THF as the solvent at –78 °C with BF_3•OEt_2 as an additive gave (*R*)-**67** in excellent yield and >99% optical purity. Using (*R*)-(triethyl)methanesulfinyl imine gave excellent selectivity and, unlike the (*R*)-*tert*-butanesulfinyl imine derivative, did not generate any undesirable odor during the acid-mediated deprotection. A chromatography-free process was demonstrated in a single vessel using commercially available **66** as a starting material (**Scheme 20**).[56] Thus, treatment of nitrile **66** with Red-Al® in toluene followed by condensation with (*R*)-TESA gave the desired sulfinyl imine. Diastereoselective addition of *i*-BuLi in the presence of BF_3•OEt_2 at –78 °C, followed by cleavage of the chiral auxiliary, afforded (*R*)-**67** in 99% enantiomeric excess. (*R*)-**67** was isolated as the D-tartrate salt in 83% overall yield, >99% enantiomeric excess, and >99.5% chemical purity.

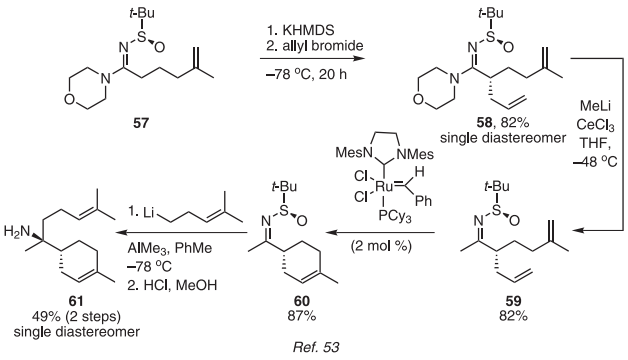
(*S*)-Cetirizine dihydrochloride is a nonsedating histamine H1-receptor antagonist used for the treatment of allergy and is currently marketed as Xyzal® in Europe. Senanayake and co-workers reported an effective asymmetric synthesis of the enantiopure key intermediate, **68**. Addition of PhMgBr to *N*-*tert*-butanesulfinyl-*p*-chlorobenzaldimine in toluene gave **68** as the major enantiomer with moderate enantiopurity (75% ee).[57] The yield and selectivity were later improved by careful tuning of the sulfinamide. Indeed, using 2,4,6-triisopropylphenylsulfinamide, **68** was obtained in 91% ee at 0 °C and 94% ee at –20 °C (**eq 11**).[58]

6. Conclusions

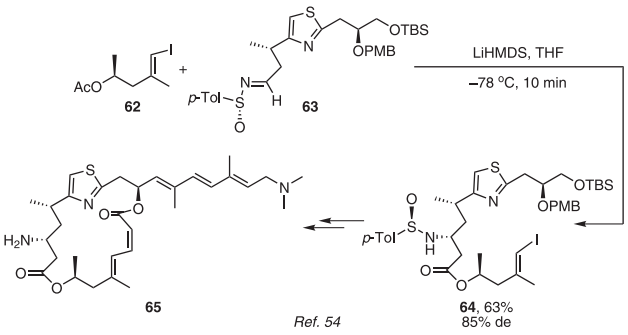
The scope of applications of chiral sulfinamides and chiral sulfoxides has grown substantially in the past five years. Furthermore, the utilization of chiral ligands based on sulfinyl imines and sulfoxides is growing at a rapid rate. However, the stereoselective synthesis of such important chiral auxiliaries has been limited to a few approaches, such as the asymmetric oxidation of prochiral sulfides and disulfides, or the use of chiral sulfinyl transfer agents. Recent progress in the general and modular synthesis of chiral sulfinamides and chiral sulfoxides using activated 1,2,3-oxathiazolidinone-2-oxides provides easy access to many structurally diverse sulfinamides and sulfoxides. Chiral sulfinamides have proven highly efficient as chiral auxiliaries in the synthesis of a variety of optically active amines, including diamines, amino alcohols, aziridines, and amino phosphonates. Structurally diverse sulfinamides are a powerful optimization tool and lead to improved yields and enhanced selectivities. In addition, chiral sulfinamides and chiral sulfoxides have been widely utilized as ligands in catalytic asymmetric processes, such as the Diels–Alder and the allylic alkylation reactions. A number of these newly developed methodologies have been successfully applied to the asymmetric synthesis of biologically active compounds and drug candidates. We anticipate that the use of this array of sulfinamides and sulfoxides will increase as these reagents become readily available. These new developments may be applied efficiently in economical and safe processes for the large-scale production of complex biologically important targets.



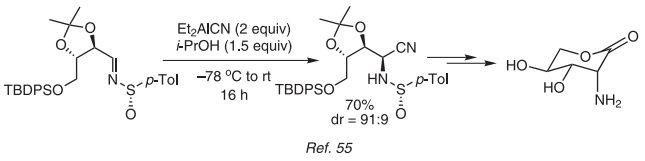
Scheme 16. Synthesis of SC-53116.



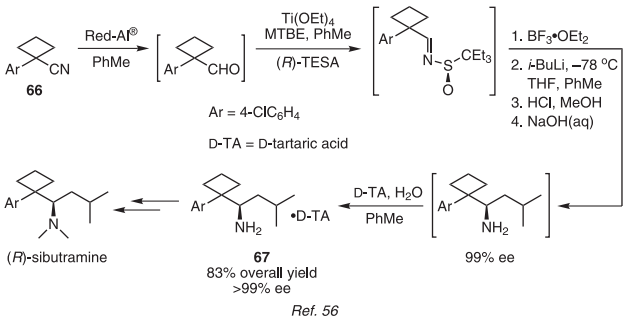
Scheme 17. Ellman's Asymmetric Synthesis of (6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene.



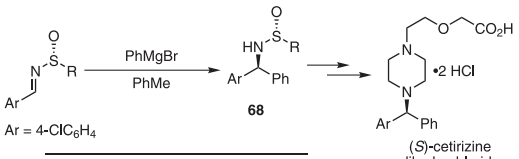
Scheme 18. Asymmetric Synthesis of (–)-Pateamine.



Scheme 19. Synthesis of Polyoxamic Acid Lactone.



Scheme 20. Asymmetric Synthesis of Sibutramine Precursor.



R	T, °C	Yield of **68**	ee of **68**
t-Bu	0	81%	75%
2,4,6-(*i*-Pr)$_3$C$_6$H$_2$	0	84%	91%
t-Bu	–20	83%	82%
2,4,6-(*i*-Pr)$_3$C$_6$H$_2$	–20	80%	94%

Ref. 57,58

eq 11

7. References and Notes

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Chris H. Senanayake was born in Sri Lanka and received his B.S. degree (First Class) there. He completed the requirements for his M.S. degree in synthetic chemistry with Professor Thomas Kinstle at Bowling Green State University. He obtained his Ph.D. degree in 1987 under the guidance of Professor James H. Rigby at Wayne State University, where he worked on the total synthesis of complex natural products, such as ophiobolanes, and completed the first total synthesis of grosshemin in the guaianolide family. He then undertook a postdoctoral fellowship with Professor Carl R. Johnson to work on the total synthesis of polyol systems, such as amphotericin B and compactin analogs, and the synthesis of C-nucleoside precursors.

In 1989, he joined The Dow Chemical Co. as a senior research chemist in the Department of Process Development, and, in 1990, accepted a position with the Merck Process Research Group as a senior research chemist. After a series of accomplishments in synthetic organic chemistry and receiving a prestigious Merck Management Award in chemistry, he was promoted to Research Fellow in 1993. In 1996, he joined Sepracor, Inc., as Director of Chemical Process Research. He was promoted to Senior Director of Chemical Process Research in 1998, and Executive Director of Chemical Process Research in 2001. He was responsible for the design and development of economical chemical processes for the commercialization of pharmaceutical drugs. In 2002, he joined Boehringer Ingelheim Pharmaceuticals, Inc., as Director of Chemical Process Research, and, in 2003, was named Director, Chemical Development. He currently leads a group of company scientists located in Ridgefield, CT, and Richmond, VA.

Dr. Senanayake's research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules and heterocycles and on catalytic, enzymatic, and mechanistic studies. He has published and lectured in the area of practical asymmetric synthesis and many disciplines of organic chemistry on how to develop drugs practically and economically in large-scale operations. He is the author of about 125 papers and patents on the design and synthesis of improved chemical entities. Dr. Senanayake is a member of the Editorial Advisory Board of *Organic Process Research & Development*.

Dhileepkumar Krishnamurthy was born in India in 1966 and received his M.Sc. degree from the Indian Institute of Technology, Bombay. He obtained his Ph.D. degree in synthetic organic chemistry in 1995 under the direction of Professor Gary Keck at the University of Utah, Salt Lake City. During this time, he contributed to the total synthesis of the antitumor antibiotic natural product rhizoxin D, and the discovery of catalytic asymmetric carbon–carbon-bond-forming reactions promoted by BINOL–titanium complexes including allylation, Mukaiyama

aldol reactions, Diels–Alder, and hetero-Diels–Alder reactions. After a brief postdoctoral stint with Professor G. E. Keck, he joined the process research group at Bristol-Myers Squibb as a Research Investigator I. He was promoted to Research Investigator II in 1998 for his accomplishments in the antiviral and oncology programs. In 1999, he joined the process research group at Sepracor, Inc., in Marlboro, MA, as a principal research scientist. At Sepracor, he and his group contributed to a number of fast-track projects and, in 2002, was named Associate Research Fellow. In late 2002, he joined Boehringer Ingelheim in Ridgefied, CT, where he is currently Associate Director for Process Research. His research interests include catalytic asymmetric synthesis and the development of practical processes for the large-scale production of biologically active compounds. He is the author of more than 30 papers and patents.

Zhi-Hui Lu was born in China in 1966. He received his B.S. degree from Peking University (1988) and his Ph.D. (1994) from the Shanghai Institute of Organic Chemistry (with Professor W. S. Zhou) and the University of Geneva, Switzerland (with Professor C. W. Jefford). He spent one year with Professor H. C. Brown at Purdue University (1995) and one-and-a-half years with Professor J. A. Marshall at the University of Virginia as a postdoctoral researcher. In 1997, he joined DuPont-Merck Pharmaceuticals as a senior research scientist in the Department of Process Research and Development, where he contributed to the development of a scalable process for the asymmetric synthesis of DMP963. In 1999, he joined Sepracor as a senior research chemist. After a series of achievements, he was promoted to principal research chemist in 2001. Following a short stay with Enanta Pharmaceuticals, he joined Boehringer Ingelheim Pharmaceuticals as a group leader in late 2002, and was promoted to his current position of Senior Principal Scientist supervising the Process Research Group in Richmond, Virginia. His research interests include the development of new synthetic processes, organometallic chemistry, and asymmetric catalysis. He is the author of about 45 papers and patents.

Zhengxu (Steve) Han was born in China. He received his B.S degree (1984) and his Ph.D. (1989) in organic chemistry from Lanzhou University. After teaching in the Department of Chemistry of Lanzhou University for two years, he moved to Tübingen University, Germany, in 1991 as a fellow of the Alexander von Humboldt Foundation. From 1993 to 1995, he worked as a postdoctoral fellow at the University of California, Berkeley, and from 1995 to 1997 at the University of Tennessee in Knoxville. In 1998, he joined the process research group at Sepracor, Inc., and, in 2005, he accepted the position of principal scientist in the process research group at Boehringer Ingelheim. His research interests center on the development of new methods for the efficient asymmetric synthesis of pharmaceutical ingredients and intermediates and of chiral amines, on asymmetric C–C- and C–N-bond-forming reactions, and on catalysis chemistry.

Isabelle Gallou was born in 1974 in Paris, France. She received her "Diplôme d'Ingénieur" in chemistry and chemical engineering in 1999 from the École Supérieure de Chimie Physique Electronique de Lyon. She obtained her Ph.D. degree in 2002 under the guidance of Professor T. V. RajanBabu at The Ohio State University, where she worked on the development of selective palladium- and rhodium-catalyzed processes for the asymmetric synthesis of structurally relevant synthons. She then joined Boehringer Ingelheim under the direct supervision of Drs. Vittorio Farina and Chris Senanayake. Her research interests include catalysis and asymmetric reactions for C–C- and C–N-bond formation, as well as the development of practical processes for the large-scale production of active pharmaceutical ingredients and intermediates.

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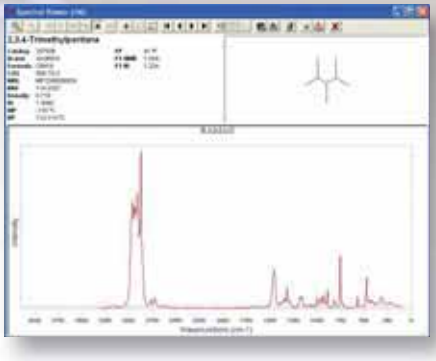

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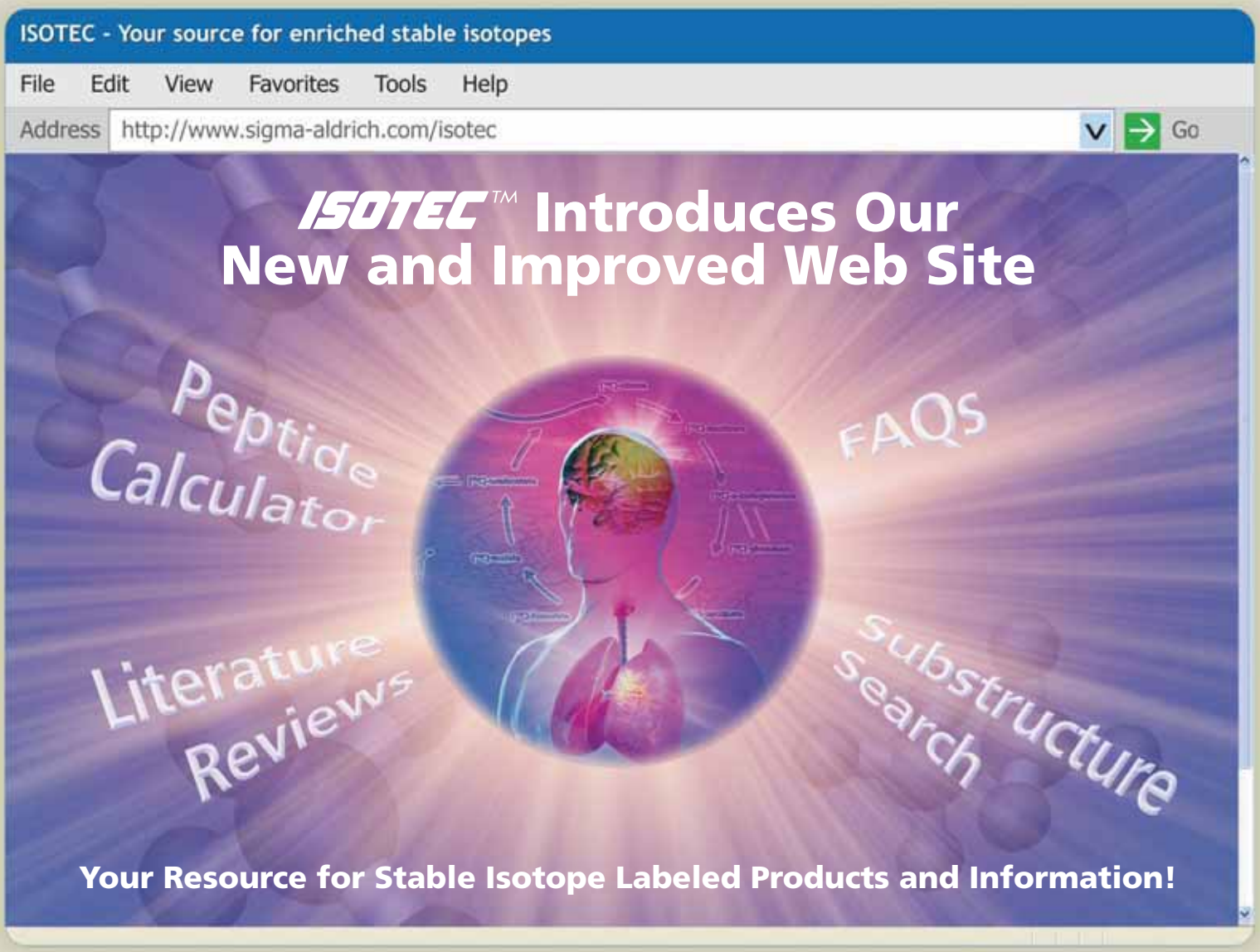

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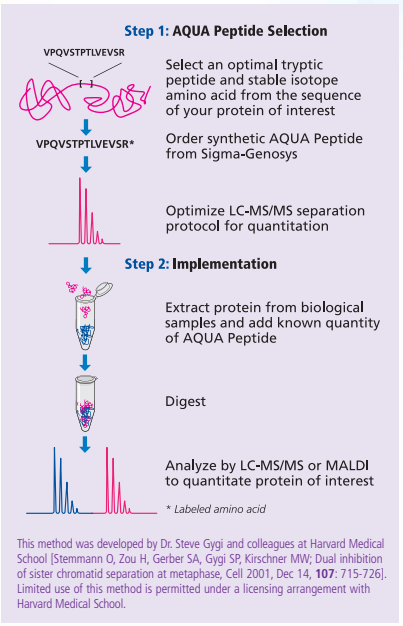

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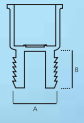

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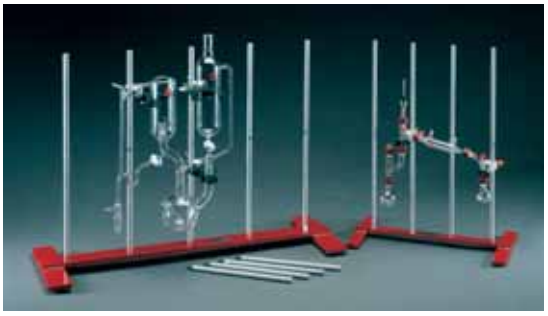

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Buchner Funnels with Modular Components

Interchangeable and replaceable components permit the use of a wide range of funnel porosities and capacities at minimal expense. It is no longer necessary to replace an entire Buchner funnel because of a clogged filter frit, or broken rim or stem.

Features

- Five interchangeable frit porosities: 4 microns up to 175 microns
- PTFE cup gasket seals edge of frit during use
- Replaceable components: frits, gaskets, funnel tops, bottoms, and connectors

Getting Started with Ver*SA*Funnel™ Is Simple

1. Order complete Ver*SA*Funnel™ assemblies below. Assembly includes funnel top, bottom, filter disc, PTFE gasket, and threaded HDPE connector.
2. Order spare components in the tables that follow.

Complete Ver*SA*Funnel™ Assemblies

Cap. (mL)	Porosity (µm)	Disc Diam (mm)	Cat. No.
30	4–8	24	**Z554251-1EA**
	10–20	24	**Z554278-1EA**
	25–50	24	**Z554286-1EA**
	70–100	24	**Z554294-1EA**
	145–175	24	**Z554308-1EA**
60	4–8	24	**Z554316-1EA**
	10–20	24	**Z554324-1EA**
	25–50	24	**Z554332-1EA**
	70–100	24	**Z554340-1EA**
	145–175	24	**Z554359-1EA**
140	4–8	50	**Z554367-1EA**
	10–20	50	**Z554375-1EA**
	25–50	50	**Z554383-1EA**
	70–100	50	**Z554391-1EA**
	145–175	50	**Z554405-1EA**
350	4–8	50	**Z554413-1EA**
	10–20	50	**Z554421-1EA**
	25–50	50	**Z554448-1EA**
	70–100	50	**Z554456-1EA**
	145–175	50	**Z554464-1EA**
600	10–20	90	**Z554472-1EA**
	25–50	90	**Z554480-1EA**
	70–100	90	**Z554499-1EA**
	145–175	90	**Z554502-1EA**
1,500	10–20	90	**Z554510-1EA**
	25–50	90	**Z554529-1EA**
	70–100	90	**Z554537-1EA**
	145–175	90	**Z554545-1EA**

Spare Filter Frits

Frits of different porosities but of the same diameter are interchangeable. Order PTFE cup gaskets separately below.

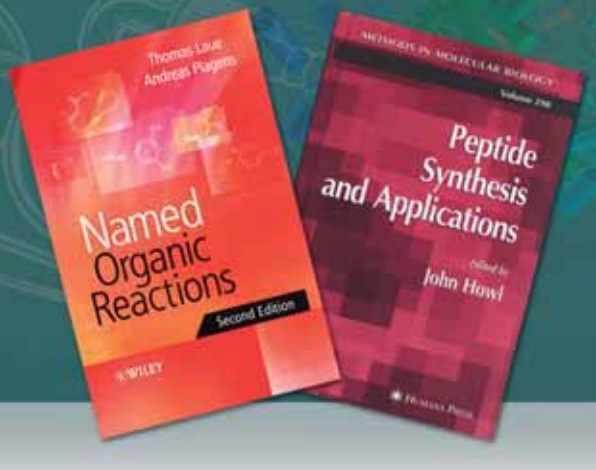
Disc Diam (mm)	Porosity (µm)	Cat. No.
24	4–8	**Z555010-1EA**
	10–20	**Z555029-1EA**
	25–50	**Z555037-1EA**
	70–100	**Z555045-1EA**
	145–175	**Z555053-1EA**
50	4–8	**Z555061-1EA**
	10–20	**Z555088-1EA**
	25–50	**Z555096-1EA**
	70–100	**Z555118-1EA**
	145–175	**Z555126-1EA**
90	10–20	**Z555134-1EA**
	25–50	**Z555142-1EA**
	70–100	**Z555150-1EA**
	145–175	**Z555169-1EA**

Replacement PTFE Cup Gaskets

Disc Diam (mm)	Cat. No.
24	**Z554987-1PAK**
50	**Z554995-1PAK**
90	**Z555002-1PAK**

Replacement Ver*SA*Funnel™ Tops, Bottoms, and Connectors

Description	Funnel Cap. (mL)	Cat. No.
Funnel top	30 and 60	**Z554863-1EA**
Funnel top	140 and 350	**Z554871-1EA**
Funnel top	600 and 1500	**Z554898-1EA**
Funnel bottom	30 and 60	**Z554901-1EA**
Funnel bottom	140 and 350	**Z554936-1EA**
Funnel bottom	600 and 1500	**Z554944-1EA**
Connector, HDPE	30 and 60	**Z554952-1EA**
Connector, HDPE	140 and 350	**Z554960-1EA**
Connector, HDPE	600 and 1500	**Z554979-1EA**



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CHEMICAL SYNTHESIS TITLES

Solid-Phase Organic Synthesis

K. Burgess, Wiley, 1999, 296pp. Hardcover. This work brings together the latest research in the field, highlighting and reviewing some of the hottest topics relevant to combinatorial chemistry, including solid-phase synthesis of natural product derivatives, synthesis of guanidine, palladium catalyzed C–C-bond-forming reactions, resin-supported capture agents and other reagents, synthesis on pins, and monitoring of supported reactions using IR.

Z421731

Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis

L. A. Paquette, Ed., Wiley, 2003, 582pp. Hardcover. As chiral reagents are key to successful asymmetric synthesis, choosing the right reagent is essential. In this handy reference, the editor gives details on how to prepare, store, and use the reagents, and provides key reactions to demonstrate where the reagents have been successfully used. This book contains comprehensive information on 226 reagents. It covers many of the optically active reagents and catalysts in use at the present time, with the overall intention to compile in manageable format as much indispensable information as possible. The selection reflects the sharp increase in demand for enantiomerically pure reagents and products. This development has been driven by synthetic organic chemists working in natural products synthesis and by medicinal chemists working on the development of enantiomerically pure drugs.

Z551430

Named Organic Reactions, Second Edition

T. Laue and A. Plagens, Wiley, 2005, 320pp. Softcover. This second edition contains concise information on 134 carefully chosen named organic reactions—the standard set for synthetic organic chemistry courses. Each reaction is detailed with clearly drawn mechanisms, references from the primary literature, well-written accounts covering the mechanical aspects of the reactions, and the details of side reactions and substrate limitations. For the second edition, the complete text has been revised and updated, and five new reactions have been added: the Baylis–Hillmann, Sonogashira, and Pummerer reactions, and the Swern oxidation and cyclopropanation.

Z703745

Principles and Applications of Asymmetric Synthesis

G.-Q. Lin, Y.-M. Li, and A. S. C. Chan, Wiley, 2001, 536pp. Hardcover. This covers more than 450 reactions, including important stoichiometric and catalytic asymmetric reactions. The first chapter reviews the basic principles, common nomenclature, and analytical methods, while the remainder of the book is organized according to reaction type. The text examines such topics as: C–C- and C–O-bond formations, asymmetric synthesis using the Diels–Alder reaction and other cyclizations, applications to the total synthesis of natural products, and the use of enzymes.

Z511811

Peptide Synthesis and Applications

J. Howl, Ed., Humana Press, 2005, 272pp. Hardcover. Experts describe in detail the methodologies of contemporary peptide synthesis and illustrate their numerous applications. Techniques presented include protocols for chemical ligation, the synthesis of cyclic and phosphotyrosine-containing peptides, lipoamino acid and sugar-conjugated peptides, and peptide purification and analysis. Additional chapters detail methodologies and instrumentation for high-throughput peptide synthesis, many different applications of peptides as novel research tools and biological probes, and the design and application of fluorescent-substrate-based peptides that can be used to determine the selectivity and activity of peptidases. A practical guide to the identification of proteins using mass spectrometric analyses of peptide mixtures is also included.

Z703826

Handbook of Organopalladium Chemistry for Organic Synthesis, 2-Volume Set

E. Negishi and A. de Meijere, Eds., Wiley, 2002, 3424pp. Hardcover. Transition metals and their complexes represent one of the most important groups of catalysts for organic reactions. Among these, palladium has emerged as one of the most versatile catalysts in modern organic synthesis. This is the first comprehensive and authoritative handbook on organopalladium reagents and catalysts. Editor Ei-ichi Negishi assembles contributions from several dozen international authorities on the use of palladium reagents and catalysts. The contents are organized by reaction type, making the two-volume set of maximum utility to the bench synthetic chemist.

Z513865

DRUG DISCOVERY TITLE

High Throughput Analysis for Early Drug Discovery

J. Kyranos, Ed., Elsevier, 2004, 350pp. Hardcover. This book offers concise and unbiased presentations by synthetic and analytical chemists, who have been involved in creating and moving the field of combinatorial chemistry into the academic and industrial mainstream. Each chapter or section begins with a description of the synthesis approach and its advantages. The description of various combinatorial and high-throughput parallel synthesis techniques provides a relevant point of entry for synthetic chemists, who need to set up appropriate characterization methods for their organizations.

Z703958

MATERIALS SCIENCE TITLES

The Chemistry of Nanomaterials: Synthesis, Properties and Applications, 2-Volume Set

C. N. R. Rao, A. Mueller, and A. K. Cheetham, Wiley-VCH, 2004, 761pp. Hardcover. The authors cover the whole spectrum of nanomaterials, ranging from theory, synthesis, properties, to characterization and application, including such new developments as: quantum dots, nanoparticles, nanoporous materials, as well as nanowires, nanotubes, and nanostructural polymers; nanocatalysis, nanolithography, and nanomanipulation; and methods for the synthesis of nanoparticles.

Z703850

Nanophysics and Nanotechnology: An Introduction to Modern Concepts in Nanoscience

E. L. Wolf, Wiley, 2004, 187pp. Softcover. Provides the first self-contained introduction to the physical concepts, techniques, and applications of nanotechnology, which should be of interest to readers grounded in college chemistry and physics. It is suitable for anyone in engineering, science, and materials science and to research workers of varied backgrounds in the interdisciplinary areas that make up nanotechnology. The author covers the latest examples of nanoscale systems, quantum concepts and effects, self-assembled nanosystems, manufacturing, and scanning probe methods of observation and fabrication, and single-electron and molecular electronics. He concludes with a look at the long-term outcomes.

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