Top Curr Chem (2015)
DOI: 10.1007/128_2015_639

Asymmetric Synthesis with Hypervalent Iodine Reagents

Ravi Kumar and Thomas Wirth

Abstract This chapter describes recent developments in stereoselective synthesis using hypervalent iodine reagents.

Keywords Hypervalent iodine · Stereoselective reactions

Contents

1 Introduction

Hypervalent iodine compounds have attracted much attention in recent years because of their unique characteristic properties to promote unprecedented and versatile reactions under mild reaction conditions. Their potential as reagents in asymmetric and even catalytic oxidative protocols has been established over the last decade. This area has been reviewed from different points of view (for recent

R. Kumar and T. Wirth (✉)
School of Chemistry, Cardiff University, Park Place, Main Building, Cardiff CF10 3AT, UK
e-mail: wirth@cf.ac.uk

reviews, see [1–11]). The astounding progress and developments made in asymmetric synthesis with hypervalent iodine compounds are discussed in this review.

2 Asymmetric Synthesis with Hypervalent Iodine Compounds

The first ever chiral hypervalent iodine compound, diphenyliodonium tartrate, was reported in 1907 by Pribram [12]. However, the use of hypervalent iodine compounds in asymmetric synthesis has only been explored over the last decade. Access to asymmetric reactions can be obtained either through the use of chiral hypervalent iodine reagents or by using achiral hypervalent iodine compounds in combination with chiral ligands. Hypervalent iodine compounds are utilized in these reactions either in stoichiometric amounts or as catalysts. Various asymmetric transformations are achieved with moderate to excellent enantioselectivity with these reagents. This review is divided into different sections based on the type of transformations involved:

1. α-Functionalization of carbonyl compounds
2. Alkene functionalization
3. Phenolic oxidation
4. Oxidation of sulfides to sulfoxides
5. Rearrangement reactions
6. Heterocyclization reactions

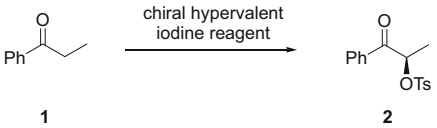
2.1 α-Functionalization of Carbonyl Compounds

Carbonyl oxidation with hypervalent iodine reagents involves the functionalization of the α-position of carbonyl compounds through the intermediacy of a hypervalent iodine enolate species. This electrophilic intermediate may be attacked by a variety of nucleophiles or undergo rearrangement or elimination [13]. Enantiomerically pure, α-substituted carbonyl compounds represent a family of derivatives important in nearly all fields of organic chemistry [14].

2.1.1 Carbon–Heteroatom Bond Formation

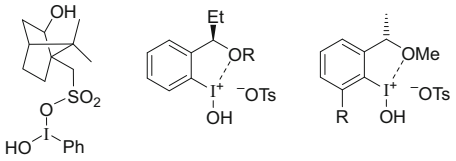
The functionalization of carbonyl compounds at the α-position represents one of the typical reactions of [hydroxy(organosulfonyloxy)iodo]arenes. As shown in Scheme 1, these reagents can be used for the α-oxytosylation of ketones such as propiophenone **1** and obtain product **2**. Encouraged by Koser's model [15, 16], Varvoglis et al. investigated the attachment of a chiral moiety to the hypervalent iodine reagent **3** (Fig. 1) [17]. This reagent **3** reacts with ketones to afford the oxysulfonylation products with good regioselectivity using non-symmetrical ketones, albeit with low stereoselectivity for all the cases investigated.

Scheme 1 Asymmetric α-oxytosylation reaction



1 **2**

Fig. 1 Chiral hypervalent iodine reagents **3–5**



3 **4** **5a** (R = OMe)
5b (R = Et)

A major development in this area was achieved by the introduction of new chiral hypervalent iodine reagents **4** and **5** (Fig. 1) [18–20]. High stereoselectivity in chiral selenium-mediated alkene oxidations, in which the selenium cation is coordinated to the oxygen atom, turned out to be the guiding concept for the development of these reagents [21, 22]. With chiral iodine(III) reagent **4** (Fig. 1), the enantioselectivity of the oxytosylation of propiophenone as shown in Scheme 1 could be improved [19]. A series of *ortho*-substituted chiral iodine(III) derivatives **5** were evaluated as stereoselective electrophilic reagents in the α-oxytosylation reaction. After optimizing the substituents in the chiral moiety and the stereoelectronic properties of the reagents **5**, as well as the reaction conditions, the product **2** was obtained with up to 40% *ee* (using **5b**) [20].

Enantioselective α-oxytosylation reactions are not limited only to the stoichiometric use of chiral iodine(III) reagents. Catalytic amounts of enantiomerically pure iodoarenes in the presence of *m*CPBA as stoichiometric oxidant with *para*-toluene sulfonic acid also gave promising results [23]. Enantiopure iodoarenes with very different structural features were optimized to afford the desired α-oxytosylated products in moderate to good enantioselectivity. A series of chiral ethers and esters were evaluated as a new class of chiral iodine catalysts [24, 25]. Promising enantioselectivities were observed using catalysts **6** (**2**: 27% *ee*), **7** (**2**: 39% *ee*) and **8** (**2**: 26% *ee*) in the α-oxytosylation of propiophenone (Fig. 2). A further enhancement of the enantiomeric excess in such reactions was highlighted by the use of 3,3′-diiodo-BINOL-fused maleimides **9**. These compounds were found to be the most efficient catalysts, leading to the formation of oxytosylated product **2** in up to 46% *ee* when used together with 1.5 equiv. of *m*CPBA and *para*-toluene sulfonic acid [26].

Chiral aryl iodides containing norephedrine or pseudo-ephedrine moieties such as **10** [27], chiral iodooxazoline catalyst **11** [28] and the spirobiindane scaffold **12** [29] were also proven to have potential towards catalytic asymmetric α-oxytosylation reactions. The best results obtained in terms of enantioselectivity of product **2** using these chiral iodine catalysts are 18% *ee* (with **10**), 48% *ee* (with **11**) and 53% *ee* (with **12**) (Fig. 3).

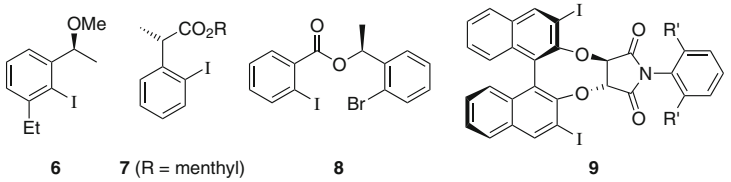


Fig. 2 Pre-catalysts **6–9** used for α-oxytosylation reactions

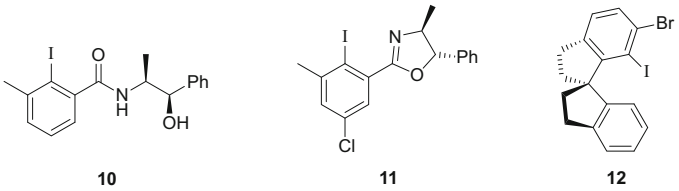
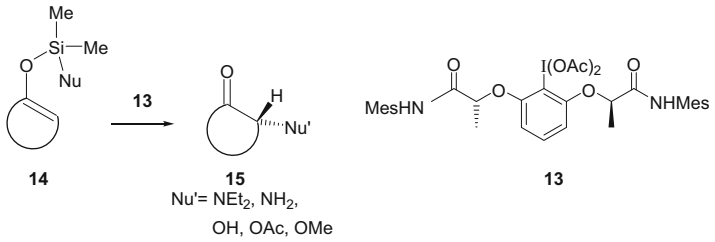


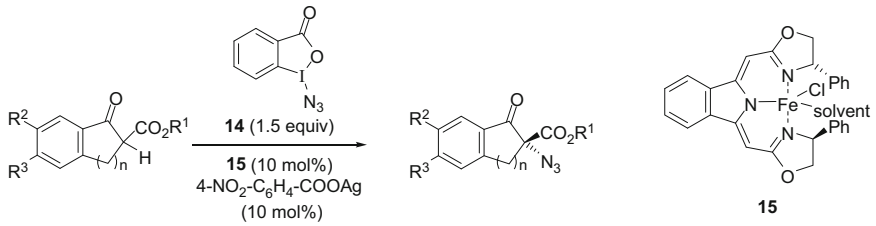
Fig. 3 Chiral aryl iodides **10–12**



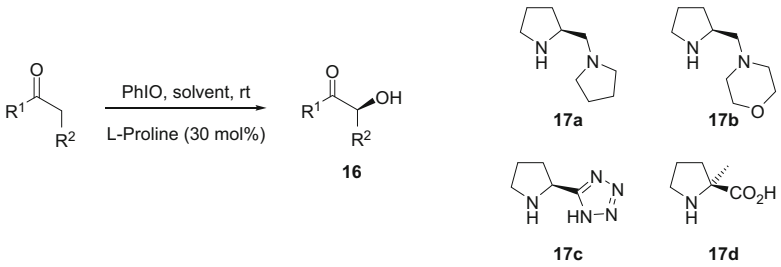
Scheme 2 Asymmetric O- and N-substitution of ketones developed by Wirth et al

Asymmetric carbon–heteroatom bond formation involving different oxygen and nitrogen nucleophiles was further rationalized using chiral hypervalent iodine reagent **13**. This asymmetric α-functionalization of carbonyl derivatives includes the concept of 'silyl temporary tethers'. The strategy developed herein allows rapid access to nitrogen- and oxygen-substituted ketones of type **15** from enol ethers **14** in a simple operation with up to 94% *ee* (Scheme 2). These findings allow novel retrosynthetic planning and a rapid assembly of structures previously accessible only by multistep sequences [30].

Hypervalent iodine reagents show excellent compatibility with organocatalysts which is demonstrated in different examples. A productive merger of iodine reagents in combination with metal catalysts and organocatalysts allowed excellent results for α-functionalizations. Gade et al. exploited this multicatalysis approach for the asymmetric azidation of β-ketoesters and 3-aryloxindoles using iodine(III) compound **14** (Scheme 3) [31]. The azidation of β-ketoesters was performed using catalytic amounts of the iron(II) chloride complex **15** and silver carboxylate as shown in Scheme 3, yielding the products in up to 93% *ee*.



Scheme 3 Enantioselective α-azidation via productive merger of iodine(III) reagents with iron catalysts

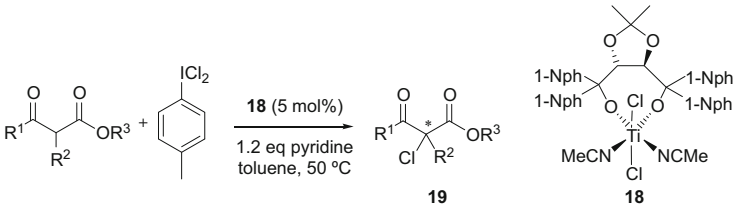


Scheme 4 Proline-catalyzed α-hydroxylation reaction

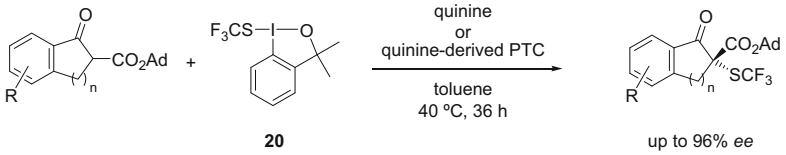
Amino acids can catalyze the biomimetic asymmetric α-oxidation of aldehydes and ketones [32, 33]. The direct proline-catalyzed asymmetric α-oxidation of ketones with iodosobenzene as stoichiometric oxidant yielded the corresponding α-hydroxylated products **16** with up to 77% *ee* [34]. Diamines **17a–d** can also be used to catalyze this transformation, albeit with moderate yields and enantioselectivities up to 63% (Scheme 4).

Catalytic asymmetric halogenation reactions are still rarely studied. Togni et al. developed the efficiency of [Ti(TADDOLato)] complexes **18** in combination with the fluorinating agent Selectfluor^{TM} in the catalytic fluorination of β-ketoesters. In 2004, this group executed the asymmetric chlorination of β-ketoesters using titanium complexes **18** with (dichloroiodo)toluene to generate enantiomerically enriched α-chlorinated products **19** (Scheme 5) [35].

The incorporation of a thiotrifluoromethyl (SCF_3) group into small molecules is of great interest to the pharmaceutical and agrochemical industries. The preparation of the electrophilic thiotrifluoromethylated hypervalent iodine reagent **20**, which was found to be quite stable in many solvents, even at elevated temperatures, was achieved by the Shen group. The authors reported the use of reagent **20** in combination with quinine or quinine-based phase transfer catalysts (PTC) in the enantioselective thiotrifluoromethylation of β-ketoesters as shown in Scheme 6 [36].



Scheme 5 Catalytic asymmetric chlorination of β-ketoesters

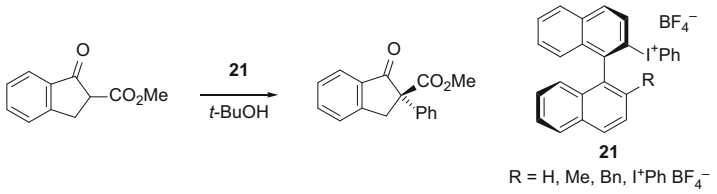


Scheme 6 Thiotrifluoromethylation reaction reported by Shen et al

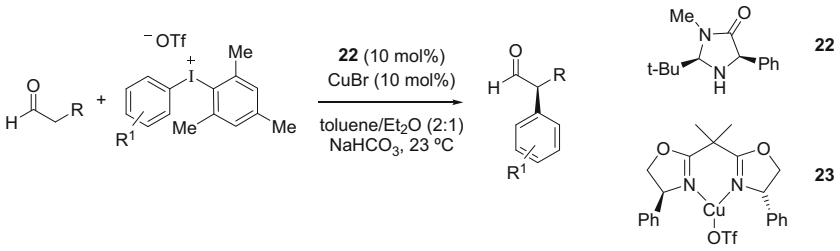
2.1.2 Carbon–Carbon Bond Formation

Stereoselective carbon–carbon bond formations with hypervalent iodine reagents are also prominently described in the literature. Direct asymmetric α-arylation reactions are not easy to perform. Ochiai et al. synthesized chiral diaryliodonium salts such as [1,1′-binaphthalen]-2-yl(phenyl)iodonium tetrafluoroborate derivatives **21** via a BF_3-catalyzed tin-λ^3-iodane exchange reaction and developed the direct asymmetric α-phenylation of enolate anions derived from cyclic β-ketoesters (Scheme 7) [37]. A beautiful example of direct asymmetric α-arylation of cyclohexanones in the course of a natural product synthesis was presented through the desymmetrization of 4-substituted cyclohexanones using Simpkin's base, followed by coupling with diaryliodonium salts [38]. Other binaphthyl iodonium salts related to **21** have also been reported [39].

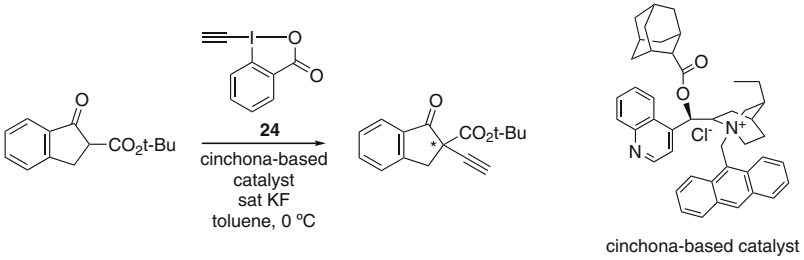
As already discussed, a productive merger of hypervalent iodine reagents with metal catalysts and organocatalysts gave interesting results in enantioselective transformations. Diaryliodonium salts in combination with copper catalysts and organocatalysts such as **22** were utilized to arylate enantioselectively a wide range of aldehyde derivatives (Scheme 8) [40]. Excellent enantioselectivity was also realized by using chiral copper catalyst **23** containing a bisoxazoline ligand in α-arylation reactions of *N*-acyloxazolidinones [41, 42]. Furthermore, scandium (III) complexes of chiral *N*,*N*′-dioxides bearing tetrahydroisoquinoline backbones were found appropriate for N-unprotected 3-substituted oxindoles (up to 99% *ee* and 99% chemical yield) [43]. The synergistic combination of iodine reagents with organocatalysts and metal catalysts is not restricted to arylation reactions and was found useful in the enantioselective α-trifluoromethylation of aldehydes [44], β-ketoesters [45] and in α-vinylation reactions [46].



Scheme 7 Direct asymmetric α-arylation using chiral diaryliodonium salts **21**



Scheme 8 α-Arylation of aldehydes using diaryliodonium salts with copper catalysts

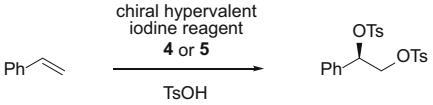


Scheme 9 Cinchona-based catalysis for enantioselective α-ethynylations

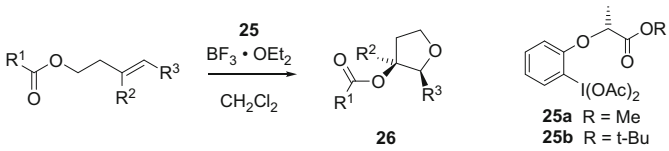
Enantioselective organocatalytic α-ethynylation reaction of β-ketoesters was investigated by Waser et al. through benziodoxolone-mediated cinchona-based catalysis using reagent **24** (Scheme 9) [47]. The products were obtained in up to 40% *ee*. The Vesely group explored a similar cinchona-based catalytic approach towards the asymmetric α-alkynylation of nucleophilic fluorocarbons [48].

2.2 Alkene Functionalization

Alkene substrates on oxidation with hypervalent iodine reagents allow various transformations depending on their structure and on the reaction conditions. Some of these reactions using chiral hypervalent iodine reagent are reported to be stereoselective. As described earlier, the Wirth group developed new chiral



Scheme 10 Dioxytosylation reactions of styrene



Scheme 11 Intramolecular oxygenation of but-3-enyl carboxylates developed by Fujita et al

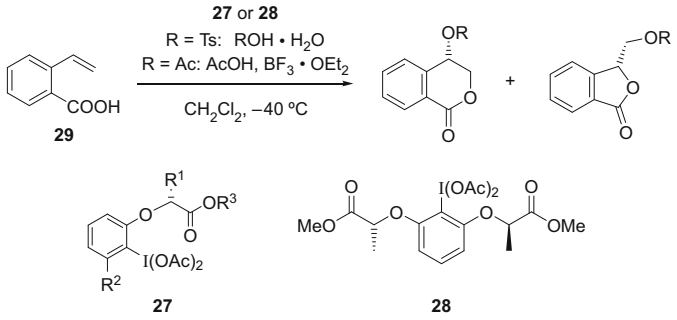
hypervalent iodine(III) reagents **4** and **5** for α-oxytosylations [18, 20–22]. Reaction of these reagents with styrene also gave promising results, leading to the formation of dioxytosylated products with enantioselectivities up to 65% (Scheme 10).

The stereoselective construction of substituted tetrahydrofurans as enantiomerically pure form is of great interest because many biologically active compounds have such oxygen heterocycles. Fujita et al. developed the synthesis of tetrahydrofuran-3-yl carboxylates **26** via intramolecular oxygenation of but-3-enyl carboxylates using lactic acid-derived chiral λ^3-iodanes **25** (Scheme 11) [49, 50]. The *endo*-selectivity achieved in this case contrasts with the *exo*-selectivity observed in the reaction with conventional oxidizing reagents. The products **26** are obtained in up to 64% *ee*.

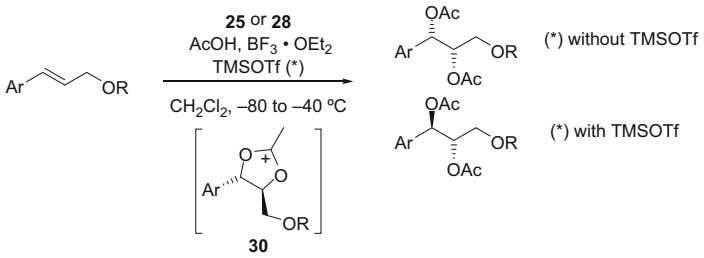
Further elaboration of this reaction principle using substrates such as 2-ethenylbenzoic acid **29** and methyl *ortho*-alkenylbenzoates provided enantiodifferentiating *endo*-selective oxylactonizations after oxidation with chiral iodine reagents **27** and **28** (Scheme 12) [51, 52]. The protocol developed here was found quite useful in the synthesis of several polyketide metabolites [53, 54]. In addition to the stoichiometric use of iodine(III) reagents, these oxylactonization reactions can also be performed using only a catalytic amount of chiral iodoarenes in presence of *m*CPBA as terminal oxidant [51]. Furthermore, changing the substrates to *ortho*-alkenylbenzamides, the intramolecular oxygenation reaction gave isochroman-1-imines via a sequence of oxidation reactions [55].

An interesting example with a switchover of the stereochemical course was observed during the enantioselective diacetoxylation of alkenes using chiral iodine (III) reagents (Scheme 13) [56]. Enantioselective Prevost and Woodward reaction products were formed through the optically active 1,3-dioxolan-2-yl cation intermediates **30**.

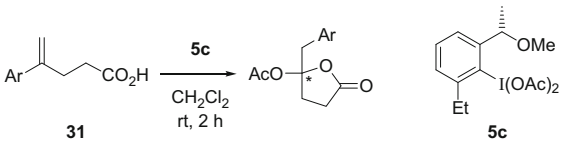
Intramolecular oxygenation reactions were also used in the asymmetric synthesis of different substituted lactone derivatives. Using chiral λ^3-iodane **5c**, lactonization of 4-aryl-4-pentenoic acids **31** gave rearranged lactones through phenonium ion participation in 56% yield, albeit in only 4% *ee* (Scheme 14) [57]. Another example of lactonization involving enantioselective



Scheme 12 *Endo*-selective oxylactonization of 2-ethenylbenzoic acid **29**



Scheme 13 Enantioselective Prevost and Woodward reactions

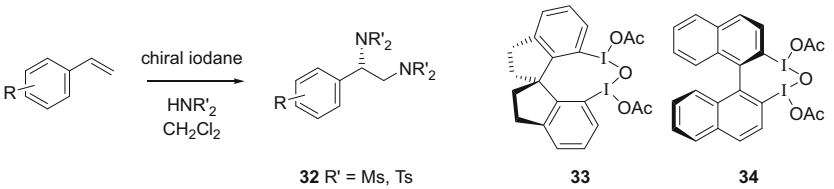


Scheme 14 Lactonization of 4-aryl-4-pentenoic acids **31**

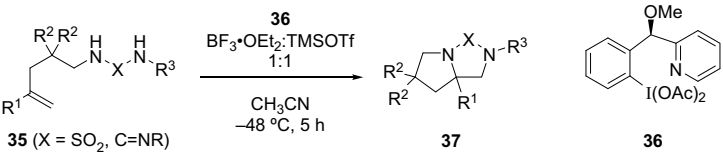
oxytrifluoromethylation of olefinic acids catalysed by copper salts gave moderate enantiomeric ratios [58].

In addition to oxygen nucleophiles, inter- as well as intramolecular asymmetric alkene oxidations using nitrogen nucleophiles were also studied. Direct asymmetric intermolecular diamination reactions using spirocyclic (**33**) [59], lactate-based (**28**) [57] or binaphthyl (**34**) [60] chiral λ^3-iodanes were investigated using different alkene substrates (Scheme 15). The intermolecular diamination reaction works well with a series of alkenes; however, styrenes represent a privileged substrate class with respect to enantioselective induction and reagent **28** was identified as the most suitable for this transformation. The products **32** are obtained in up to 95% *ee* and they can be recrystallized to >99% *ee*.

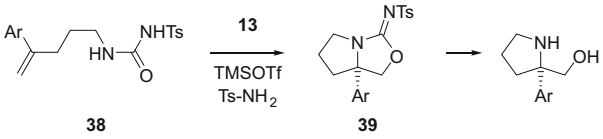
For intramolecular diaminations, a novel chiral hypervalent iodine reagent **36** was successfully synthesized and used in the enantioselective cyclization of guanidine and sulfodiamine derivatives **35** to give cyclized products **37**, which can be



Scheme 15 Intramolecular diaminations reported by Muñiz et al



Scheme 16 Intramolecular diamination of guanidine and sulfodiamines **35**

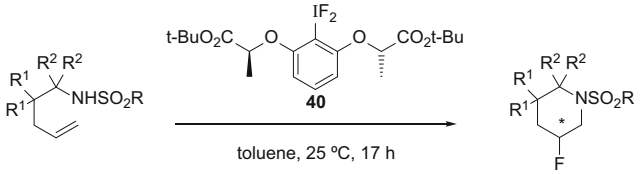


Scheme 17 Enantioselective synthesis of isourea derivatives **39**

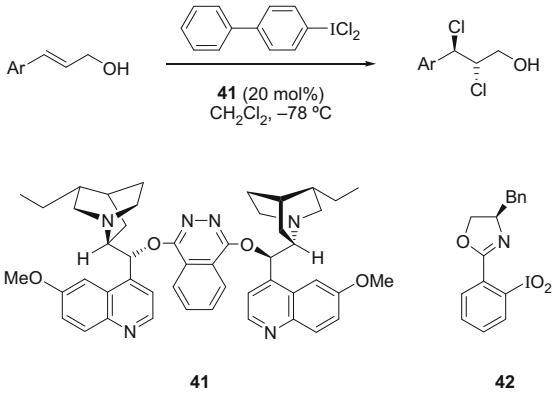
easily reduced to the corresponding diamines (Scheme 16) [61]. This reaction was initially performed using chiral lactate-based iodine(III) reagents, but the cyclized product was only obtained with up to 52% *ee*. The novel hypervalent iodine reagent **36** with an efficient coordination of the pyridine nitrogen to the iodine atom is responsible for selectivities up to 96% *ee*. Cyclizations of *N*-tosylated urea derivatives **38** using chiral λ^3-iodane **13** were also successfully studied for the synthesis of aminoalcohols (up to 96% *ee*) via isourea derivatives **39** (Scheme 17) [62].

A similar approach was used for intramolecular aminofluorination of unactivated olefins mediated by the chiral hypervalent iodine(III) reagent **40** leading to the enantioselective formation of fluorinated piperidine ring derivatives (Scheme 18) [63]. Reagent **40** performs the aminofluorination of pentenamines showing total regioselective control for the 6-*endo* cyclization products in favour of piperidine formation in excellent enantiomeric excesses (up to 81% *ee*, 99% *ee* after recrystallization).

Despite tremendous advances in the development of chiral methods, asymmetric alkene dichlorination remains one of the challenges. This reaction was successfully achieved for *trans*-cinnamyl alcohols as substrates using (dichloroiodo)arenes in combination with dimeric cinchona alkaloid derivatives **41** leading to products with up to 85% *ee* (Scheme 19) [64]. Chiral iodine(V) reagent **42** in combination with pyridine hydrobromide led to the dibromination of β-methylstyrene in only 3% *ee* [65].



Scheme 18 Regioselective 6-*endo* fluorinated cyclisation of pentenamines

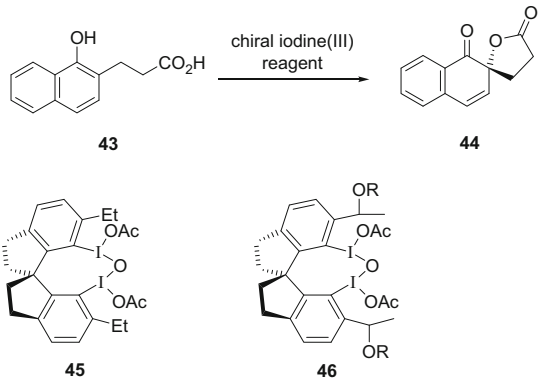


Scheme 19 Asymmetric dichlorination of *trans*-cinnamyl alcohols

2.3 Phenolic Oxidation

Phenolic oxidations are pivotal steps frequently involved in the biosynthesis of natural products, which possess a variety of important biological activities. Therefore, a continuing interest exists in such transformations, in particular in asymmetric oxidative protocols. Kita et al. performed asymmetric dearomatization of naphthols **43** mediated by chiral hypervalent iodine(III) reagents, **33** and **45** having a rigid spirobiindane backbone (Scheme 20) [66, 67]. A series of other *ortho*-functionalized spirobiindane reagents of type **46** were synthesized. Intramolecular oxidative substitution of **43** afforded five-membered spirolactone **44** with good levels of enantioselectivity (up to 92% *ee*). Conformationally flexible iodoarenes employed in this study produced almost racemic products. Catalytic use of these chiral catalysts with *m*CPBA as cooxidant afforded the chiral spirolactones without detrimental effects on the *ee* values.

Further advancements in the Kita oxidative spirolactonization of naphthols were explored by Ishihara et al. using catalytic amounts of rationally-designed conformationally flexible C_2-symmetric iodoarenes **47** and **48** (Fig. 4) [68–70]. The iodine (III) reagents, generated in situ, were expected to exhibit intramolecular either n to σ* interactions between the electron-deficient iodine(III) center and the Lewis-basic group or intramolecular hydrogen bonding interaction between the acidic hydrogen and the ligand which should allow a suitable chiral environment to give selectivity in the reaction.



Scheme 20 Enantioselective oxidative dearomatisation of naphthols **43** developed by Kita et al

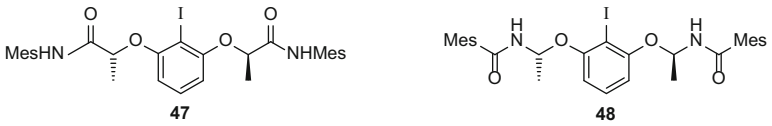
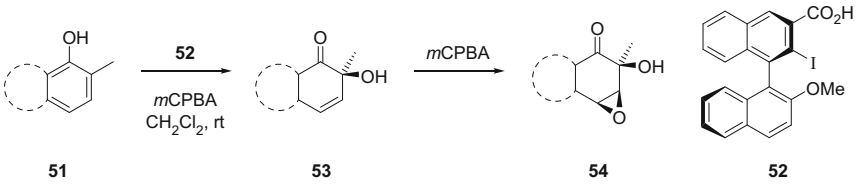


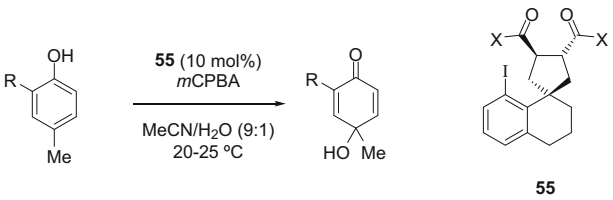
Fig. 4 C_2-symmetric iodoarenes **47** and **48**

Scheme 21 Diels–Alder dimerisations of alkylphenols **49**



Scheme 22 Asymmetric hydroxylative phenol dearomatization

The oxidation of *ortho*-alkylphenols **49** with iodine(V) derivatives of type **42** containing chiral oxazoline moieties led to asymmetric [4+2] Diels–Alder dimerizations. The *ortho*-alkylphenols **49** were transformed into *ortho*-quinol dimers **50** with significant levels of asymmetric induction (up to 77% *ee*) (Scheme 21) [71]. Similar substrates **51** were subjected to hydroxylative phenol dearomatization to give *ortho*-quinol products **53** (Scheme 22) [72]. The protocol was devised making use of the chiral iodoarene **52** in combination with *m*CPBA; however, an



Scheme 23 Stereoselective phenolic dearomatization using chiral aryl iodide catalysts **55**

excessive use of the cooxidant in this reaction afforded directly the epoxide product **54** in up to 91% yield.

New chiral aryl iodide catalysts **55** were prepared by Harnerd et al. for assessing the stereoselective phenolic dearomatization. Catalysts **55** derived from 8-iodotetralone and tartaric acid could be used to synthesize enantioenriched *para*-quinols (up to 60% *ee*) from phenols as shown in Scheme 23 [73].

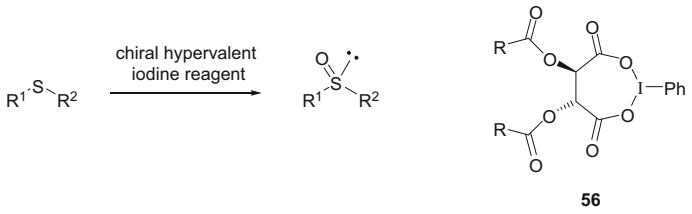
2.4 Oxidation of Sulfides to Sulfoxides

Chiral sulfoxides find immense use, reflecting a wide interest in both convenient auxiliaries in asymmetric synthesis and products with biological properties containing a chiral sulfinyl group. Since the pivotal report of Imamoto and Koto [74], who discovered that chiral hypervalent iodine reagents of the suggested structure **56** are capable of asymmetrically oxidizing prochiral sulfides to sulfoxides, other research groups have also emphasized the utilization of chiral iodine reagents towards these transformations. Imamoto and coworkers generated chiral iodine(III) reagents **56** in situ by the reaction of iodosylbenzene and different L-tartaric anhydrides and realized the asymmetric oxidation of sulfides (Scheme 24).

Despite the potential of chiral iodinanes, asymmetric synthesis using these reagents was rarely explored until 1990. Preparation of chiral iodinanes **57** (Fig. 5) by ligand exchange reaction between menthol and Koser's reagent [PhI(OH)OTs] was found quite useful for achieving asymmetric sulfide oxidation [75]. Chiral λ^3-iodane **1**, used by Varvoglis et al. to assess asymmetric α-oxysulfonylation of carbonyl compounds, also gave good results in the sulfide oxidation.

Reactions of chiral λ^5-iodanes, amino acid-derived benziodazole oxides **58** [76], (*S*)-proline based reagents **59** [77], and iodylarenes **60** bearing ester motives [78] with non-symmetric sulfides to give asymmetric sulfoxide formation further recognized the importance of such transformations.

Not only do chiral hypervalent iodine reagents have the potential for such conversions, achiral iodanes in combination with chiral auxiliaries can also be used in asymmetric oxidative protocols. The Kita group performed the controlled oxidation of sulfides to sulfoxides using iodoxybenzene ($PhIO_2$) in a cationic reversed micellar system. High chemical yields and good stereoselectivities



Scheme 24 Asymmetric oxidation of sulfides to sulfoxides

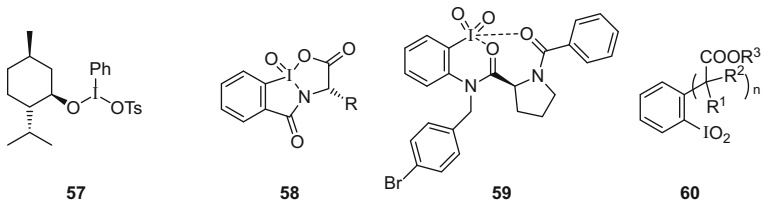


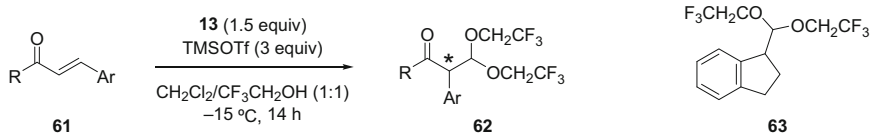
Fig. 5 Structures of chiral iodine reagents **57–60**

(up to 72% *ee*) were achieved by employing a catalytic amount of cetyltrimethylammonium bromide (CTAB) and a tartaric acid-based chiral source [79]. The solubilization and activation of $PhIO_2$ was achieved by adding catalytic amounts of CTAB and the tartaric acid derivative. In a similar approach, the use of water and catalytic amounts of magnesium bromide for sulfoxide formation was investigated, although with only moderate enantioselectivities [80].

SIBX is a non-explosive formulation of the λ^5-iodane 2-iodoxybenzoic acid (IBX) stabilized by benzoic acid. This reagent combination can be used as a suspension in various organic solvents to oxidize sulfides to sulfoxides. Most yields were comparable to those obtained using IBX or other iodanes such as PhIO and $PhIO_2$. The use of a chiral tartaric acid-based source in addition to SIBX gave asymmetric sulfoxide formation with moderate enantioselectivities [81].

2.5 Rearrangement Reactions

The nature of hypervalent iodine(III) compounds to react as electrophiles and then act as excellent leaving groups makes them highly suitable reagents for generating cationic intermediates, which can either react directly with nucleophiles or lead to rearranged products under ring expansion, ring contraction, or aryl migration. The Wirth group published a seminal report on the stereoselective rearrangements of chalcones **61** with high enantioselectivities mediated by chiral hypervalent iodine reagents **13** (Scheme 25) [82]. The enantioselectivity of this transformation was closely related to the choice of the solvent and Lewis acid employed. Under optimal reaction conditions, the stereoselective rearrangement to **62** was observed in



Scheme 25 Stereoselective rearrangement of chalcones **61**

enantioselectivities of up to 97%. A first enantioselective ring contraction of dihydronaphthalene was also performed using this method to afford indene acetal **63** with up to 70% enantiomeric excess.

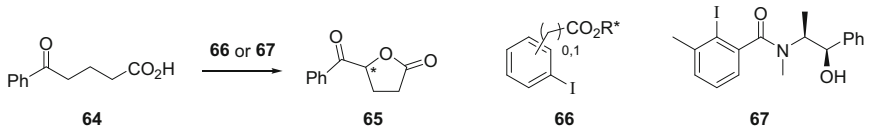
2.6 Heterocyclization Reactions

The enantioselective lactonization of 5-oxo-5-phenylpentanoic acids **64** was studied using chiral λ^3-iodanes **66** to yield 5-benzoyldihydrofuran-2(3*H*)-ones **65**, albeit with low *ee* values (Scheme 26) [83]. Scope of this asymmetric lactonization process was further studied by employing other chiral aryl iodides such as **67** [84].

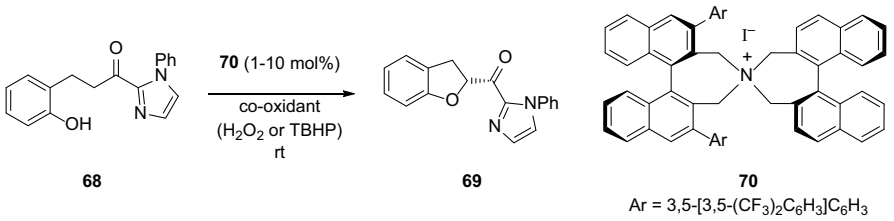
The optically active 2-acyl-2,3-dihydrobenzofuran skeleton is a key structure in several biologically active compounds. The asymmetric oxidation of ketophenols **68**, catalyzed by in situ generated chiral quaternary ammonium (hypo)iodite salts **70**, with hydrogen peroxide as cooxidant, opened up a new enantioselective, metal-free route to 2-acyl-2,3-dihydrobenzofurans **69** (Scheme 27) [85]. The substituents at the 3,3′-positions of the binaphthyl moiety of the salt **70** played an important role in the enantioselectivity as well as in the chemical yield of the reaction. The products are formed in up to 96% *ee*.

Aziridines are key structural motifs present in natural products such as mitomycins and azinomycins and versatile building blocks which can undergo various useful transformations. Hypervalent iodine-mediated intramolecular aziridinations of allylic carbamates and reaction of *N*-tosyliminophenyliodinane (PhI = NTs) with double bonds have been reported to be efficient and practical routes to access these three-membered rings. Allylic carbamates **71** undergo enantioselective aziridine formation on oxidation with chiral binaphthyl hypervalent iodine compound **72** (Scheme 28) [86].

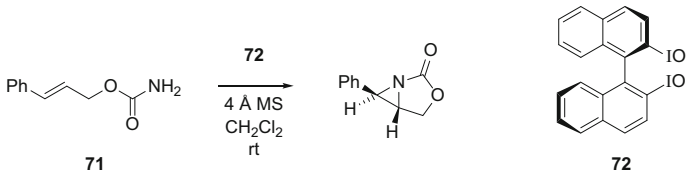
Reactions of *N*-tosyliminophenyliodinanes (PhI=NTs) as nitrene source with alkenes in the presence of chiral ligands also present a valuable method to achieve asymmetric aziridination reactions. Cinnamate esters **73** yield enantiomeric aziridinate products in good selectivities on reaction with chiral bisoxazolines **23** and *N*-tosyliminophenyliodinanes in the presence of copper salts (Scheme 29) [87]. Biaryl Schiff bases **74** can also be used as ligands in the enantioselective aziridination of cinnamate esters, chromenes and styrenes [88]. Chiral C_2-symmetric salen-type ligands **75** were also found to be highly effective for the



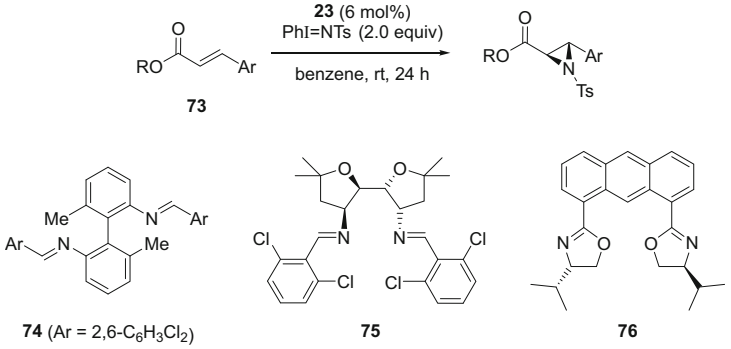
Scheme 26 Enantioselective lactonization of 5-oxo-5-phenylpentanoic acid **64**



Scheme 27 Chiral quaternary ammonium (hypo)iodite salt-mediated asymmetric oxidation of ketophenols **68**



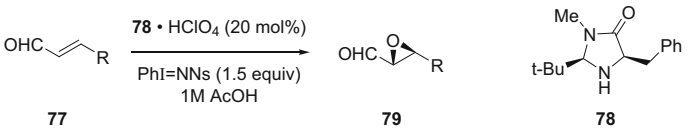
Scheme 28 Intramolecular aziridination of allylic carbamates **71**



Scheme 29 Stereoselective aziridination of cinnamate esters **73**

enantioselective control of the copper-catalyzed asymmetric aziridination of cinnamate esters [89].

Copper complexes of bisoxazoline ligands [90] such as **76** with a more rigid structure and other optimized bisoxazoline ligands [91] can asymmetrically aziridinate chalcone substrates with high enantioselectivities.



Scheme 30 Organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes **77**

Epoxides can also be accessed asymmetrically using hypervalent iodine reagents in combination with imidazolidinone catalysts **78** (Scheme 30). The methodology developed by MacMillan et al. includes participation of hypervalent iodine reagent in a 1,4-heteroconjugate addition reaction for the organocatalytic, asymmetric epoxidation of α,β-unsaturated aldehydes **77**. This organocatalytic reaction allows for the enantioselective formation of epoxides **78** from a wide array of electronically and sterically diverse α,β-unsaturated aldehydes [92].

3 Outlook

This review summarizes important aspects of hypervalent iodine compounds in asymmetric synthesis. Some of the transformations have been achieved with excellent enantioselectivities, thus opening up a new era in this field. Several oxidation reactions such as the functionalization of carbonyls, phenolic oxidation, sulfide oxidation and alkene functionalization have been achieved with good enantiocontrol. Seminal contributions have inspired remarkable subsequent studies, but considerable effort is still needed to enfold new reactivities, develop efficient catalytic asymmetric protocols and further improve the enantiocontrol of these processes. The generation of new families of chiral compounds containing polyvalent iodine atoms can tackle important challenges and their application to other disciplines, such as total synthesis or pharmaceutical chemistry. Furthermore, the search for new chiral ligands which can be utilized in combination with achiral hypervalent iodine reagents can also make significant contributions in this area in the future.

References

1. Berthiol F (2015) Synthesis 47:587
2. Dong DQ, Hao SH, Wang ZL, Chen C (2014) Org Biomol Chem 12:4278
3. Romero RM, Wöste TH, Muñiz K (2014) Chem Asian J 9:972
4. Singh FV, Wirth T (2014) Chem Asian J 9:950
5. Harned AM (2014) Tetrahedron Lett 55:4681
6. Parra A, Reboredo S (2013) Chem Eur J 19:17244
7. Singh FV, Wirth T (2013) Synthesis 45:2499
8. Brown M, Farid U, Wirth T (2013) Synlett 24:424

9. Gonzàlez DF, Benfatti F, Waser J (2012) ChemCatChem 4:955
10. Liang H, Ciufolini MA (2011) Angew Chem Int Ed 50:11849
11. Merritt EA, Olofsson B (2011) Synthesis 517
12. Pribram R (1907) Justus Liebigs Ann Chem 351:481
13. Moriarty RM, Prakash O (1999) Org React 54:273
14. Marigo M, Jørgensen K (2006) Chem Commun 2001
15. Koser GF, Wettach RH (1977) J Org Chem 42:1476
16. Koser GF, Relenyi AG, Kalos AN, Rebrovic L, Wettach RH (1982) J Org Chem 47:2487
17. Hatzigrigoriou E, Varvoglis A, Bakola-Christianopoulou M (1990) J Org Chem 55:315
18. Wirth T, Hirt UH (1997) Tetrahedron Asymmetry 8:23
19. Hirt UH, Spingler B, Wirth T (1998) J Org Chem 63:7674
20. Hirt UH, Schuster MFH, French AN, Wiest OG, Wirth T (2001) Eur J Org Chem 1569
21. Wirth T (1995) Angew Chem Int Ed Engl 34:1726
22. Wirth T, Kulicke KJ, Fragale G (1996) J Org Chem 61:2686
23. Richardson RD, Page TK, Altermann S, Paradine SM, French AN, Wirth T (2007) Synlett 538
24. Altermann SM, Richardson RD, Page TK, Schmidt RK, Holland E, Mohammed U, Paradine SM, French AN, Richter C, Bahar AM, Witulski B, Wirth T (2008) Eur J Org Chem 5315
25. Farooq U, Schäfer S, Ali Shah AUH, Freudendahl DM, Wirth T (2010) Synthesis 1023
26. Brenet S, Berthiol F, Einhorn J (2013) Eur J Org Chem 8094
27. Rodríguez A, Moran WJ (2012) Synthesis 1178
28. Guilbault A, Basdevant B, Wanie V, Legault CY (2012) J Org Chem 77:11283
29. Yu J, Cui J, Hou XS, Liu SS, Gao WC, Jiang S, Tian J, Zhang C (2011) Tetrahedron Asymmetry 22:2039
30. Mizar P, Wirth T (2014) Angew Chem Int Ed 53:5993
31. Deng QH, Bleith T, Wadepohl H, Gade LH (2013) J Am Chem Soc 135:5356
32. Córdova A, Sundén H, Engqvist M, Ibrahem I, Casas J (2004) J Am Chem Soc 126:8914
33. Sundén H, Engqvist M, Casas J, Ibrahem I, Córdova A (2004) Angew Chem Int Ed 43:6532
34. Engqvist M, Casas J, Sundén H, Ibrahem I, Córdova A (2005) Tetrahedron Lett 46:2053
35. Ibrahim H, Kleinbeck F, Togni A (2004) Helv Chim Acta 87:605
36. Wang XQ, Yang T, Cheng XL, Shen QL (2013) Angew Chem Int Ed 52:12860
37. Ochiai M, Kitagawa Y, Takayama N, Takaoka Y, Shiro M (1999) J Am Chem Soc 121:9233
38. Aggarwal VK, Olofsson B (2005) Angew Chem Int Ed 44:5516
39. Brown M, Delorme M, Malmedy F, Malmgren J, Olofsson B, Wirth T (2015) Synlett 26 (in press)
40. Allen AE, MacMillan DWC (2011) J Am Chem Soc 133:4260
41. Harvey JS, Simonovich SP, Jamison CR, MacMillan DWC (2011) J Am Chem Soc 133:13782
42. Bigot A, Williamson AE, Gaunt MJ (2011) J Am Chem Soc 133:13778
43. Guo J, Dong SX, Zhang YL, Kuang YL, Liu XH, Lin LL, Feng XM (2013) Angew Chem Int Ed 52:10245
44. Allen AE, MacMillan DWC (2010) J Am Chem Soc 132:4986
45. Deng QH, Wadepohl H, Gade LH (2012) J Am Chem Soc 134:10769
46. Skucas E, MacMillan DWC (2012) J Am Chem Soc 134:9090
47. González DF, Brand JP, Waser J (2010) Chem Eur J 16:9457
48. Kamlar M, Putaj P, Vesely J (2013) Tetrahedron Lett 54:2097
49. Fujita M, Okuno S, Lee HJ, Sugimura T, Okuyama T (2007) Tetrahedron Lett 48:8691
50. Fujita M, Ookubo Y, Sugimura T (2009) Tetrahedron Lett 50:1298
51. Fujita M, Yoshida Y, Miyata K, Wakisaka A, Sugimura T (2010) Angew Chem Int Ed 49:7068
52. Shimogaki M, Fujita M, Sugimura T (2013) Eur J Org Chem 7128
53. Fujita M, Mori K, Shimogaki M, Sugimura T (2012) Org Lett 14:1294
54. Fujita M, Mori K, Shimogaki M, Sugimura T (2013) RSC Adv 3:17717
55. Takesue T, Fujita M, Sugimura T, Akutsu H (2014) Org Lett 16:4634
56. Fujita M, Wakita M, Sugimura T (2011) Chem Commun 47:3983
57. Boye AC, Meyer D, Ingison CK, French AN, Wirth T (2003) Org Lett 5:2157

58. Zhu R, Buchwald SL (2013) Angew Chem Int Ed 52:12655
59. Röben C, Souto JA, González Y, Lischynskyi A, Muñiz K (2011) Angew Chem Int Ed 50:9478
60. Röben C, Souto JA, Escudero-Adàn EC, Muñiz K (2013) Org Lett 15:1008
61. Mizar P, Laverny A, El-Sherbini M, Farid U, Brown M, Malmedy F, Wirth T (2014) Chem Eur J 20:9910
62. Farid U, Wirth T (2012) Angew Chem Int Ed 51:3462
63. Kong W, Feige P, Haro T, Nevado C (2013) Angew Chem Int Ed 52:2469
64. Nicolaou KC, Simmons NL, Ying Y, Heretsch PM, Chen JS (2011) J Am Chem Soc 133:8134
65. Ngatimin M, Gartshore CJ, Kindler JP, Naidu S, Lupton DW (2009) Tetrahedron Lett 50:6008
66. Dohi T, Maruyama A, Takenaga N, Senami K, Minamitsuji Y, Fujioka H, Caemmerer SB, Kita Y (2008) Angew Chem Int Ed 47:3787
67. Dohi T, Takenaga N, Nakae T, Toyoda Y, Yamasaki Y, Shiro M, Fujioka H, Maruyama A, Kita Y (2013) J Am Chem Soc 135:4558
68. Uyanik M, Yasui T, Ishihara K (2010) Tetrahedron 66:5841
69. Uyanik M, Yasui T, Ishihara K (2010) Angew Chem Int Ed 49:2175
70. Uyanik M, Yasui T, Ishihara K (2013) Angew Chem Int Ed 52:9215
71. Boppisetti JK, Birman VB (2009) Org Lett 11:1221
72. Quideau S, Lyvinec G, Marguerit M, Bathany K, Ozanne-Beaudenon A, Buffeteau T, Cavagnat D, Chénedé A (2009) Angew Chem Int Ed 48:4605
73. Volp KA, Harned AM (2013) Chem Commun 49:3001
74. Imamoto T, Koto H (1986) Chem Lett 967
75. Ray DG III, Koser GF (1990) J Am Chem Soc 112:5672
76. Zhdankin VV, Smart JT, Zhao P, Kiprof P (2000) Tetrahedron Lett 41:5299
77. Ladziata U, Carlson J, Zhdankin VV (2006) Tetrahedron Lett 47:6301
78. Altermann SM, Schäfer S, Wirth T (2010) Tetrahedron 66:5902
79. Tohma H, Takizawa S, Watanabe H, Fukuoka Y, Maegawa T, Kita Y (1999) J Org Chem 64:3519
80. Tohma H, Takizawa S, Morioka H, Maegawa T, Kita Y (2000) Chem Pharm Bull 48:445
81. Ozanne-Beaudenon A, Quideau S (2006) Tetrahedron Lett 47:5869
82. Farid U, Malmedy F, Claveau R, Albers L, Wirth T (2013) Angew Chem Int Ed 52:7018
83. Farooq U, Schäfer S, Shah AA, Freudendahl DM, Wirth T (2010) Synthesis 1023
84. Rodríguez A, Moran WJ (2012) Synthesis 44:1178
85. Uyanik M, Okamoto H, Yasui T, Ishihara K (2010) Science 328:1376
86. Deng QH, Wang JC, Xu ZJ, Zhou CY, Che CM (2011) Synthesis 2959
87. Evans DA, Faul MM, Bilodeau MT, Anderson BA, Barnes DM (1993) J Am Chem Soc 115:5328
88. Gillespie KM, Sanders CJ, O′Shaughnessy P, Westmoreland I, Thickitt CP, Scott P (2002) J Org Chem 67:3450
89. Wang X, Ding K (2006) Chem Eur J 12:4568
90. Xu J, Ma L, Jiao P (2004) Chem Commun 1616
91. Ma L, Du DM, Xu J (2005) J Org Chem 70:10155
92. Lee S, MacMillan DWC (2006) Tetrahedron 62:11413