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Synthetic Methods

of Organic Chemistry

Vol. 67

Advice to the User

General Remarks

New methods for the synthesis of organic compounds and improvements of known methods are being recorded continuously in this series.

Reactions are classified on a simple though purely formal basis by symbols, which can be arranged systematically. Thus searches can be performed without knowledge of the current trivial or author names (e.g. 'Oxidation' and 'Friedel-Crafts reaction').

Users accustomed to the common notations will find these in the subject index (see page 330). By consulting this index, use of the classification system may be avoided. It is thought that the volumes should be kept close at hand. The books should provide a quick survey, and obviate the immediate need for an elaborate library search. Syntheses are therefore recorded in the index by starting materials and end products, along with the systematic arrangement for the methods. This makes possible a sub-classification within the reaction symbols by reagents, a further methodical criterion. Complex compounds are indexed with cross reference under the related simpler compounds. General terms, such as synthesis, replacement, heterocyclics, may also be brought to the attention of the reader.

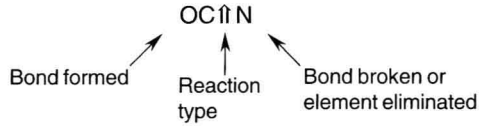
A brief review (*Trends* section, see page XI), stresses highlights of general interest and calls attention to key methods too recent to be included in the body of the text.

The abstracts are limited to the information needed for an appraisal of the applicability of a desired synthesis. In order to carry out a particular synthesis it is therefore advisable to have recourse to the original papers or, at least, to an abstract journal. In order to avoid repetition, selections are made on the basis of most detailed description and best yields whenever the same method is used in similar cases. Continuations of papers already included will not be abstracted, unless they contain essentially new information. They may, however, be quoted at the place corresponding to the abstracted papers. These supplementary references (see page 387) make it possible to keep abstracts of previous volumes up-to-date.

Syntheses that are divided into their various steps and recorded in different places can be followed with the help of the notations such as *startg. m. f.* (starting material for the preparation of ...).

Method of Classification

Reaction Symbols. As summarized in the Systematic Survey (page XXVI), reactions are classified firstly according to the bond formed in the synthesis, secondly according to the reaction type, and thirdly according to the bond broken or the element eliminated. This classification is summarized in the reaction symbol, e.g.

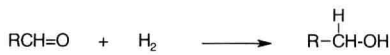


The first part of the symbol refers to the chemical bond formed during the reaction, expressed as a combination of the symbols for the two elements bonded together, e.g. HN, NC, CC. The order of the elements is as follows:

H, O, N, Hal (Halogen), S, Rem (Remaining elements), and C.

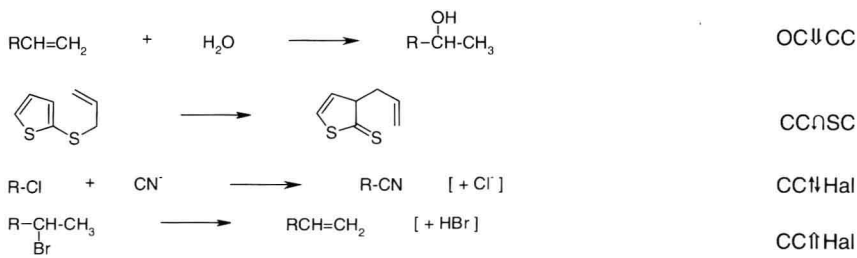
Thus, for the formation of a hydrogen-nitrogen bond, the notation is HN, not NH.

If two or more bonds are formed in a reaction, the 'principle of the latest position' applies. Thus, for the reduction



in which both hydrogen-oxygen and hydrogen-carbon bonds are formed, the symbol is HC⇓OC and not HO⇓OC.

The second part of the symbol refers to the reaction type. Four types are distinguished: addition (⇓), rearrangement (∩), exchange (⇅), and elimination (⇑), e.g.



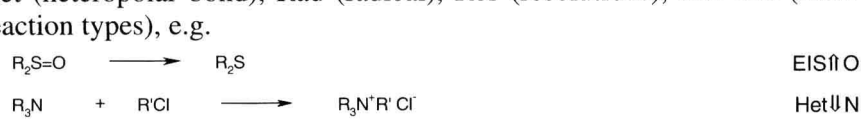
Monomolecular reactions are either rearrangements (∩), where the molecular weight of the starting material and product are the same, or eliminations (⇑), where an organic or inorganic fragment is lost; bimolecular and multicomponent reactions are either additions (⇓), such as intermolecular

Diels-Alder reactions, Michael addition and 1,4-addition of organometallics, or exchanges (↓↑), such as substitutions and condensations, where an organic or inorganic fragment is lost.

The last part of the symbol refers to the essential bond broken or, in the case of exchange reactions and eliminations, to a characteristic fragment which is lost. While the addition symbol is normally followed by the two elements denoting the bond broken, in the case of valency expansion, where no bonds are broken, the last part of the symbol indicates the atom at which the addition occurs, e.g.

For addition, exchanges, and eliminations, the 'principle of the latest position' again applies if more than one bond is broken. However, for rearrangements, the most descriptive bond-breakage is used instead. Thus, for the thio-Claisen rearrangement depicted above, the symbol is CC∩SC, and not CC∩CC.

Deoxygenations, quaternizations, stable radical formations, and certain rare reaction types are included as the last few methods in the yearbook. The reaction symbols for these incorporate the special symbols El (electron pair), Het (heteropolar bond), Rad (radical), Res (resolutions), and Oth (other reaction types), e.g.



The following rules simplify the use of the reaction symbols:

1. The chemical bond is rigidly classified according to the structural formula without taking the reaction mechanism into consideration.

2. Double or triple bonds are treated as being equivalent to two or three single bonds, respectively.

3. Only stable organic compounds are usually considered: intermediates such as Grignard compounds and sodiomalonic esters, and inorganic reactants, such as nitric acid, are therefore not expressed in the reaction symbols.

Reagents. A further subdivision, not included in the reaction symbols, is based on the reagents used. The sequence of the reagents usually follows that of the periodic system. Reagents made up of several components are arranged according to the element significant for the reaction (e.g. $KMnO_4$ under Mn, NaClO under Cl). When a constituent of the reagent forms part of the product, the remainder of the reagent, which acts as a 'carrier' of this

constituent, is the criterion for the classification; for example, phosphorus is the carrier in a chlorination with PCl_5 and sodium in a nitrosation with $NaNO_2$.

High-Coverage Searches

A search through *Synthetic Methods* provides a selection of key references from the journal literature. For greater coverage, as for bibliographies, a supplementary search through the following publications is suggested:

Derwent Reaction Service[1]. Designed for both current awareness and retrospective retrieval. Its monthly publication, the *Derwent Journal of Synthetic Methods*, covers the journal and patent literature, and provides 3,000-3,600 abstracts of recently published papers annually.

Access is available in-house via RX-JSM to over 100,000 reactions, including the data in all the abstracts in *Synthetic Methods*, while online access to data from 1980 is provided on STN as DJSMONLINE.

Science Citation Index[2]. For which *Synthetic Methods* serves as a source of starting references. This is particularly useful for accessing papers quoting details of a particular method which has been included in these volumes from a preliminary communication.

Chemical Abstracts Service[3]. References may not be included in *Synthetic Methods* (1) to reactions which are routinely performed by well known procedures; (2) to subjects which can be easily located in handbooks and indexes of abstracts journals, such as the ring system of heterocyclics or the metal in case of organometallic compounds, and (3) to inadequately described procedures, especially if yields are not indicated.

References to less accessible publications such as those in the Chinese or Japanese language are usually only included if the method in question is not described elsewhere.

[1] Thomson Scientific Ltd., 14 Great Queen Street, London WC2B 5DF, England.

[2] Thomson Scientific Inc., Philadelphia, Pa., USA.

[3] Chemical Abstracts Service, Columbus, Ohio, USA.

Trends and Developments in Synthetic Organic Chemistry 2005

The *Trends* section of Volume *66* opened with organocatalysis[1]. This time, the focus is on another developing facet of catalysis, which might broadly be generalized as *dual catalysis*. It embraces several elements, of which *bifunctional catalysis, cooperative catalysis and tandem catalysis* are the principle protagonists. The first, developed largely by Shibasaki et al. in the late nineties (*57,* 238), features dual activation of the electrophilic and nucleophilic components of an asym. bimolecular reaction with a chiral reagent, recently adapted to asym. 1,4-hydrocyanation with gadolinium(III) 1,1′-binaphthoxides possessing both Lewis acidic and basic sites[2]. The principle has also been extended to *bifunctional organocatalysts,* in which a basic residue, such as an amino group, is accompanied in the same molecule by a *quasi*-Lewis acidic function, such as a urea or thiourea group, which activates the electrophile *by hydrogen bonding*. This is exemplified by dynamic kinetic resolution on alcoholysis of azlactones in the presence of *tert*-aminothioureas, as a new route to chiral α-amino acids[3]. For asym. Michael addition of trisubst. C-nucleophiles to 1,1-nitroethylene derivs., however, a bifunctional *Cinchona* alkaloid is preferred, the nitro group being activated through hydrogen bonding to a phenolic residue[4]. More familiar in this context is bifunctional catalysis with chiral *bimetallic* complexes, such as Shibasaki's alkali metal aluminum 1,1′-bi-2-naphthoxides (*51*, 309), through which the carbonyl residue of an electrophile is activated by the Lewis acidic aluminum while the lithium cation facilitates deprotonation of the nucleophile. This methodology has now been extended to an asym. phosphine-mediated Baylis-Hillman reaction with a chiral lithium boron 1,1′-bi-2-naphthoxide[5], whereas more subtle electrostatic activation through an intermediate zwitterionic species is at play in a recent asym. cyclopropanation of enals with sulfonium ylids in the presence of a chiral bifunctional indoline-2-carboxylic acid[6]. The second dual aspect, cooperative catalysis, features activation of electrophile/nucleophile partners by *two* catalysts, as illustrated in a valuable review on dual catalytic activation with a chiral Lewis acid and an amine as base[7]. Not entirely unrelated is dual activation in the asym. synthesis of quaternary α-cyanoketones from N-silylketenimines and carboxylic acid anhydrides: here, Fu's planar-chiral ferrocenyl-fused 4-aminopyridine activates the anhydride with liberation of carboxylate anion, which in turn activates the silylketenimine as a nitrile anion prior

to coupling with the generated N-acylpyridinium ion[8]. For the best of both worlds, let us say *bifunctional cooperative catalysis*, dual activation of the electrophile/nucleophile partners is effected in close proximity by a hydrogen-bonding organocatalyst and a cooperating amine separately grafted to the *same* silica surface: the advantages are fine tuning through concentration and spacial adjustment, in combination with a facile work-up[9]. Bimetal cooperative catalysis is another manifestation, as illustrated in the synthesis of N-heterocyclic ketones by coupling the corresponding N-heterocyclic aldehydes with halides: a reaction which ordinarily will not respond to a single catalyst. Here, ruthenium and palladium act in concert: the aldehyde function being initially activated by ruthenium through chelation, followed by Ru→Pd transmetalation prior to coupling with the electrophile[10]. Further cooperative effects are evident in *acid/base-assisted* catalysis: principally Lewis base-assisted Lewis acid catalysis and, more topically, Lewis acid-assisted Brønsted acid catalysis[11]. The latter has been admirably reviewed under the concept of 'designer acids'[12], while the relatively new aspect of Lewis acid-assisted Lewis acid catalysis is exemplified in a recent asym. Diels-Alder reaction wherein $SnCl_4$ (at 0.5 mol%) significantly enhances the Lewis acidity of the boron atom in chiral 1,3,2-oxazaborolidines and, at the same time, generates a more robust complex[13]. The third element of 'dual catalysis', namely *tandem catalysis*[14], is of more recent origin, featuring a single catalyst, or a combination of mutually compatible catalysts, in a *one-pot* conversion involving the sequencing of two mechanistically distinct reactions. In one recent manifestation, the synthesis of α-(benzofuran-2-yl)carboxylic acid esters is performed with the aid of $Pd(PPh_3)_4$ and PdI_2 as co-catalysts, the former effecting an initial O-deallylation, after which the latter takes over to complete a carbonylative ring closure[15]. Perhaps more dramatic is a ruthenium-catalyzed dehydrogenative asym. intramolecular Diels-Alder reaction of dienylhydroxamic acids. Here, a ruthenium(IV) oxo complex, generated *in situ* from a chiral ruthenium(II) salen complex, initially dehydrogenates the hydroxamic acid residue, while the liberated ruthenium(II) complex (as a hydrate) activates [through hydrogen bonding] the formed acylnitroso residue prior to intramolecular cycloaddition[16]. By the same token, the asym. synthesis of γ-subst. alcohols from enones can be carried out with a chiral hydridoruthenium tetrahydridoborate which catalyzes both the initial asym. 1,4-addition and the ensuing reduction of the keto group[17]. A tandem route to indoles from *o*-dihalides and prim. amines has also been devised with Pd and

Cu as co-catalysts, the initial Sonogashira coupling preceding N-arylation and intramolecular hydroamination of the alkyne[18]. Closely allied to tandem catalysis is *simultaneous* catalysis at essentially different sites of a molecule by the same catalyst. This is nicely illustrated in a recent hydrogenation of phthalimides with $[RuCl_2(p\text{-cymene})]_2$, which effects both hydrogenation of the benzene ring and partial deoxygenation of the imide residue in one hit[19]. Conditions for simultaneous cyclopropanation of an alkene residue and Reformatsky reaction at a keto group are also available[20].

Turning to classical base catalysis, it is interesting that an old friend, 1,8-diazabicyclo[5.4.0]undec-7-ene, being inexpensive, air-stable and readily removable, serves as catalyst for Michael addition [of alcohols and amines][21] as well as *metal- and solvent-free* aldol-type condensation and Michael-type addition[22], while LiOAc as Lewis base is wide-ranging in facilitating syntheses by and via nucleophilic addition to imines[23]. In the arena of Brønsted acid catalysis, however, triflimide is evolving as an alternative to less friendly metal-based Lewis acids[24], while chiral, cyclic phosphoric acid diesters are a positive gain in asym. acid catalysis[25]. Two other methods come to mind in this context: the first being a new synthesis of α,β-diaminocarboxylic acid esters by Lewis acid-catalyzed addition of N-alkylideneglycinates *to enamines*[26]; and the second reflecting another up-and-coming mode of catalysis, namely nucleophilic *carbene catalysis*, illustrated by an interesting redox-type conversion of α,β-ethylenealdehydes to carboxylic acid derivs.[27]

In asym. transition metal catalysis[28], a variety of new chiral P-ligands is now available for rhodium-catalyzed asym. homogeneous hydrogenation. Enhancement of activity, stability and enantioselectivity is the *raison d'être,* as with chiral *o*-phosphinoaryl biphenyl-2,2′-diyl phosphites for the asym. hydrogenation of α-benzyloxy-α,β-ethylenephosphonic acid esters[29]; *hybrid* 1,1′-binaphthyl-2,2′-diyl N-[α-(2-phosphinoferrocenyl)alkyl]phosphoramidites, however, are useful alternatives for the critical asym. hydrogenation of dehydroamino acid esters[30], as also are monodentate, *P-chiral* 1,1′-binaphthalene-2,2′-diyl phosphoramidites, where matching of axial and P-chirality offers scope in the recently devised combinatorial procedure for asym. hydrogenation (s. *64,* 36)[31]. Rigid 9,9′-spirobifluorenyldi(phosphines) having a large dihedral angle are notable for ruthenium-catalyzed asym. hydrogenation of α,β-ethylenecarboxylic acids at very low catalyst loadings (0.1-0.01 mol%)[32], while robust, air-stable, axially-chiral 2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridyl (Cy-P-Phos) is especially

effective for the iridium-catalyzed asym. hydrogenation of quinolines *in polyethylene glycol dimethyl ether*, rivalling ionic liquids in facilitating recovery and recycling of the catalyst[33]. More noteworthy, perhaps, is the application of chiral iridium bis(Δ^2-oxazolin-4-yl)imidazolidin-2-ylidene complexes for the asym. hydrogenation of 1,3-dienes, where enantioselectivity approaches 99% with high diastereoselectivity for the reduction of both double bonds[34]. In ruthenium-catalyzed asym. hydrogenation of β-ketocarboxylic acid esters, bulky, electron-rich 6,6′-bis(diarylphosphino)-2,2′,3,3′-bis(methylenedioxy)biphenyls (SEGphos ligands) are valuable alternatives to Noyori-type binaphthyl ligands[35], whereas P-chiral bi(benzo[*c*]phospholenyls) are effective for rhodium-catalyzed asym. hydrogenation of aminoketones[36]. In the commercially important sphere of asym. hydroformylation, where the design of efficient chiral di(phosphines) is also at a premium, one recently reported family outsmarts all others, namely chiral *o*-bis(1,2,4-diazaphospholan-4-yl)-benzenes, which offer high regioselectivity and enantioselectivities up to 96% under mild conditions at catalyst loadings as low as *0.004%*[37]. Not to been outdone, palladium-catalyzed asym. C-α-alkylation, another 'old chestnut' (updates s. *48,* 772s*67*), has also advanced on several fronts, notably with chiral *o*-(Δ^2-oxazolin-2-yl)phenyl biphenyl-2,2′-diyl phosphites as ligands, which can be readily modified to create smaller and more flexible chiral pockets for the conversion of both hindered and unhindered substrates with enantioselectivities up to 99%[38]. A mechanistically unusual palladium-catalyzed O-allylation of carboxylic acids has also evolved, courtesy of a chiral, *palladacyclic* 2-(Δ^2-oxazolin-2-yl)cyclopentadienylpalladium complex which facilitates delivery of the allyl residue from allyl trichloroacetimidate via coordination of palladium to the imino nitrogen atom[39]. A *non-basic,* decarboxylative procedure is also available for the asym. C-α-allylation of ketones via *intramolecular* delivery of the allyl residue from an intermediate allyl enol carbonate[40], while an allyl shift by [2.3]-sigmatropic rearrangement is central to a new asym. synthesis of α-allyl-α-aminocarboxylic acid esters from chiral, sultam-based quaternary ammonium ylids [without the benefit of transition metal catalysis][41]. Continuing with the sigmatropic theme, note also a novel asym. aza-Claisen rearrangement with a chiral Δ^2-oxazolin-2-ylferrocenylpalladacyclic, featuring, as above[39], an unusual bonding of palladium to the cyclopentadienyl residue[42]. Asym. catalysis with chiral main group and transition metal salen complexes has paid many dividends through the years, and is developing unabated, as illustrated by four new methods: an asym. synthesis of α,α-disubst.

ketones from tin(IV) enolates with chiral chromium salen complexes[43]; the kinetic resolution of epoxides on hydrolysis using chiral trialkylaluminum-linked cobalt(III) salen complexes[44]; the application of chiral manganese salen complexes immobilized on porous silica through phenylsulfonyl linking groups (with higher enantioselectivities by comparison with the homogeneous procedure)[45]; and asym. Friedel-Crafts-type 1,4-addition of N-heterocyclics with chiral aluminum salen and bis(salen) complexes[46]. In the asym. synthesis of β-aminocarbonyl compds. by Mannich reaction, chiral dinuclear niobium(III) complexes (based on *tridentate* 3-(*o*-hydroxybenzyl)-1,1′-bi-2-naphthol)[47] and chiral aquapalladium di(phosphine) complexes[48] both afford enantioselectivities up to 99%. In asym. 1,4-addition, where copper-catalyzed syntheses with dialkylzincs is a central theme (updates s. *52*, 297s*67*), the generation of chiral quaternary carbon centres by 1,4-addition to *acyclic* 1,1-nitroethylene derivs. has been effected with chiral amino acid-based phosphines[49]. For asym. 1,4-addition to β-subst. enones, however, dialkylzinc compds. have given way to more acidic trialkylaluminums with chiral phosphoromonoamidites as ligand[50]. A highly enantioselective intermolecular Stetter-type 1,4-addition has also been recorded by addition of aroylsilanes to α,β-ethylenecarboxylic acid amides using a TADDOL-derived metallophosphite as catalyst[51]. Perhaps more remarkable is the ligand-accelerated asym. 1,4-addition of α,β-acetyleneboronic acid esters to enones, thanks to (S)-3,3′-diiodo-1,1′-bi-2-naphthol functioning rather as tartrate ligands in Sharpless epoxidation[52]. With reference to asym. 1,2-addition of Si-nucleophiles, air- and moisture-resistant SEGphos ligands again rear their head in the CuF_2-catalyzed addition of weakly nucleophilic aryl- and vinyl-silanes to aldehydes[53], while the asym. addition of allylsilanes to aldehydes has been effected with chiral polymer-based cyclic phosphoric acid triamides as Lewis base[54]. Returning to asym. organocatalysis, proline-based asym. aldol condensation (*58,* 245) has been adapted *iteratively* to the synthesis of polyketide sugars with enantioselectivities exceeding 99%[55]. A more complex peptidyl prolinamide is even more enantioselective than proline itself[56], while (S)-2-triflylaminomethylpyrrolidine is preferred for asym. organocatalyzed Michael addition of aldehydes or ketones to 1,1-nitroethylene derivs.[57] Interestingly, asym. organocatalyzed α-sulfenylation of aldehydes can also be conducted directly using a chiral 2-α-siloxypyrrolidine as catalyst[58], whereas face-selective α-hydroxylation of ketones can be secured with either L-proline or [for the enantiomer] with a chiral diamine as ligand in the presence of an oxidant[59]. Pursuing

the theme of asym. organocatalyzed α-aminooxylation[60], an alternative Brønsted acid-catalyzed route to chiral α-aminooxyketones has been devised by addition of nitrosobenzene to *enamines* with achiral mandelic acid as auxiliary, whereas the regioisomeric α-hydroxylaminoketones are available with TADDOL instead[61]. Organocatalysis with chiral 4-imidazolidones (*65,* 445) has also developed, two research groups having simultaneously and independently reported the quite remarkable, *metal free,* biomimetic reduction of trisubst. α,β-ethylenealdehydes to the corresponding chiral aldehydes with Hantzsch ester as reductant[62]. Chiral cyclic quaternary ammonium salts, familiar as phase transfer catalysts in asym. C-α-alkylation (*58,* 353), have also been in the news again, the latter methodology being accelerated in the presence of an *achiral* crown ether or ammonium salt as co-catalyst to improve extraction of alkaline hydroxide into the organic phase[63]. The first asym. phase transfer-catalyzed nucleophilic α-arylation [with activated ar. fluorides] has also been reported with cinchoninium salts as catalyst[64]. Among the more unusual asym. syntheses to materialize in recent months, perhaps a special reference might be given to four contenders: the metal-free asym. 1,2-addition of electron-rich and heteroaromatic arenes to benzylhydrazones mediated by a chiral, Lewis acidic 2-chloro-1,3,2-oxazasilacyclopentane[65]; a Pd-catalyzed asym. hydrosilylation of alkenes with an *Si-chiral* organosilicon hydride[66]; a Pd-catalyzed asym. iodination of unactivated hydrocarbon groups substituted by Δ^2-oxazolin-2-yl groups as stoichiometric auxiliary[67]; and an asym. synthesis of sec. benzyl alcohols and benzylamine analogs from chiral benzylsulfonium ylids via B→C-alkyl migration of intermediate chiral organoboranes[68]. And lastly, in the context of asym. synthesis, an overview of the 'hidden chirality' of enolates deserves a mention[69], as does an unusual instance of reversal of face-selectivity in C-α-alkylation by merely adjusting the concentration of base[70]; however, face-selectivity in the asym. synthesis of α-branched amines by Rh-catalyzed 1,2-addition of arylboronic acids to imines is largely dependent on the nature of the N-function (sulfinyl *vs.* phosphinyl) as well as the associated P-ligand[71].

The above-outlined organocatalytic routes have much to offer from an environmental ('green') perspective, largely because a metal catalyst is not required. Note also, in this respect, the application of polycyclic tetraaminoethylenes as mild, super-SET reducing agents, being cleaner than the familiar tri-*n*-butyltin hydride for reductive ring closures of ethylenehalides (cf. *29,* 970) and the reductive dehalogenation of aryl and alkyl iodides[72]. Coupling of electron-rich aryl sulfonates and

phosphates with nucleophiles (allylsilanes and arenes) via photochemical heterolysis of the Ar-O bond is another invaluable metal-free procedure, which, furthermore, does not require a base and is compatible with aqueous media[73]. There is also a recent reference to a mild, neutral, metal-free *syn*-selective cleavage of epoxides and N-tosylaziridines with phenols via aryl boronates[74], as well as an economical, mild, and reagent-free Nazarov cyclization, facilitated under microwave irradiation in weakly Lewis-acidic ionic liquids[75].

Continuing with the theme of environmentally friendly ionic liquids[76], a special reference might be given to novel phosphonium ionic liquids, remarkable in that they support reactions involving strong bases, such as Grignard reagents[77], while *axially chiral ionic liquids* have been designed as potentially active chiral media[78]. *Ionic tagging* of reagents and catalysts is a further ploy to facilitate recovery and recycling, as illustrated by a recent Baylis-Hillman reaction in protic media with an imidazolium-tagged quinuclidine deriv.[79] This is further exemplified in the development of a readily recyclable imidazolium-tagged, chiral dichlororuthenium(II) N-sulfonyl-1,2-diamine, being superior in activity (even after 3 cycles) than the parent untagged Noyori complex for the asym. transfer-hydrogenation of aryl ketones in ionic liquids[80]. Ionic tagging of inorganic supports is another feature, as reflected in an efficient heterogeneous epoxidation with aq. H_2O_2 in the presence of a polyoxotungstate ionically immobilized by an imidazolium cation tagged to a silica surface[81]. The emergence of alternative ['green'] media, such as ionic liquids, also brings to mind the discovery of low-melting, non-toxic and inexpensive 3-component solvent systems based on sugars, e.g. sorbitol-urea-ammonium chloride, which are catalytic in their own right and have the potential of inducing asymmetry[82]. Water, however, still remains as the ultimate 'green' medium, supporting and/or accelerating a variety of diverse reactions ordinarily conducted in less friendly organic solvents. Several instances come to mind: radical deoxygenation of alcohols and radical 1,4-addition in the presence of a tetraalkylammonium hypophosphite and a water-soluble initiator[83]; the intramolecular insertion of diazo compds. into the C-H bond with water-soluble, readily recyclable (10 times!) $Rh_2(OAc)_4$[84]; hydrogenation of alkenes under mild conditions with a readily recyclable, highly active, amphiphilic, polymer-based palladium nanocatalyst[85]; water-accelerating Claisen rearrangement[86]; and water-accelerating asym. Rh-catalyzed hydrogenation, where the stability of the ligand (EtDuPHOS) and improvement in the recovery of the catalyst are a bonus[87].

Among the plethora of recent reviews on transition metal catalysis[88], timely surveys on catalytic C-O, C-N and C-C bond formation, and in particular on incorporating alkyl groups by cross-coupling, are, perhaps, the most welcome. For Pd-catalyzed N-arylation of prim. amino groups with [het]aryl chlorides, the robust and highly active ferrocenyldi-(phosphine), JosiPHOS, is the ligand of choice at catalyst loadings as low as *0.001 mol%*[89], while Heck arylation has developed with the emergence of copper-bronze as catalyst in ionic liquids[76], and with a hydroxyl-directed intramolecular Heck arylation with desymmetrization, whereby an enantiotopic *exocyclic* allyl group is generated at a quaternary site through the agency of a chiral di(phosphine) as ligand[90]. In Negishi coupling, the first asym. coupling with an *alkyl* electrophile has been reported under nickel catalysis with a chiral bis(Δ^2-oxazoline) as ligand[91], while a *copper-free* Sonogashira coupling is now possible in water under aerobic conditions[92]. A nickel-catalyzed Kumada-type coupling of *prim*-alkylmagnesium bromides has also been realized with neopentyl arenesulfonates in place of the traditional ar. halides or triflates[93], and a new diaryl synthesis is available based on Fe(III)-catalyzed cross-coupling of chloromagnesium aryl(cyano)cuprates with aryl iodides[94]. After the publication of generalized procedures for Stille (*67,* 469) and Suzuki (*67,* 459) coupling, there seemed little scope for further refinement. A nickel-catalyzed Stille coupling with *unactivated sec*-alkyl halides is, nonetheless, more than welcome[95], as is the design of highly active, phosphine-free, robust thiosemicarbazones as ligands for Suzuki coupling (affording TONs up to 40, 000 at 0.001 mol% for coupling with ar. bromides or chlorides)[96]; a new family of air-stable *o*-(dicyclohexylphosphino)benzamides is also available for coupling unactivated and/or hindered ar. chlorides[97]. For the synthesis of 6-aryl-2-deoxynucleo(s/t)ides, however, arylboronic acids are more efficiently coupled with fluorine, organothio or sulfonyl as leaving group[98], while a Suzuki diaryl coupling in aq. media is reported with a moisture-resistant di-μ-chlorodipalladate(2-) as catalyst under microwave enhancement[99]. Arylboronic acids have also featured recently in other contexts, such as a new oxidative synthesis of α,β-disubst. (Z)-stilbenes from acetylene derivs.[100], and in ring closures of acetylenealdehydes and enynes[101]. Here, reaction is initiated by arylrhodation of the alkyne group followed by intramolecular carborhodation of the appended unsaturation. Rather more unusual among transition metal-catalyzed conversions is a mechanistically unique palladium-catalyzed intramolecular cross-coupling of aryl iodides with allyl acetates[102]. An unusual rhodium-

catalyzed reductive coupling of chiral epoxides with aldehydes has also recently been reported to provide chiral glycol monoethers with >95% regioselectivity[103]. Alternative syntheses under molybdenum catalysis are always worth considering as, for example, the hydrostannylation of 2-allenealcohols with $Mo(CO)_3(t\text{-BuNC})_3$, where regioselectivity is superior to that reported under palladium catalysis[104]; note also unusual applications of molybdenum in a high valency state *as reducing agents*, exemplified by the hydrosilylation of oxo compds. with MoO_2Cl_2[105]. There was a time, of course, when molybdenum and tungsten were central to alkene metathesis, but nowadays it is almost exclusively the province of ruthenium-carbene catalysis. Developments and applications in this arena are legion but two new devices come to mind. In one, cross-metathesis of olefins is facilitated by a template effect occasioned by tethering the substrates with oligoamide residues, thereby minimising the possibility of homocoupling[106]. In the second, an intramolecular ene-yne metathesis is facilitated by initial interaction of the alkyne residue with a metathetically inactive (η^6-arene)ruthenium phosphine-complex to generate it's own ruthenium carbene catalyst prior to ring closure[107].

In the critically important functionalization of hydrocarbons, a high-yielding hydroxylation has been effected in ionic liquids with friendly H_2O_2 and readily recyclable $MeReO_3$ as catalyst[108], while a high-yielding chemoselective monobromination has been demonstrated under mild conditions with Br_2 and inexpensive, readily recoverable MnO_2[109]. A remarkable oxidation of ketones with iodine in alcoholic media has also been reported as a direct route to α-hydroxyketals[110], and an equally remarkable Fe(III)-Fe(IV) manifold is central to the aerobic oxidation of primary alcohols to aldehydes with the development of novel iron(III) macrocyclic tetraamido complexes[111]. An interesting Cu(I)-catalyzed dehydrogenative coupling of secondary amines with aliphatic nitro compds. has also materialized[112], along with an oxidative coupling of ketones with pyrroles[113]. Note also a simple α-acoxylation of aldehydes with N-*tert*-butyl-O-benzoylhydroxylamine hydrochloride via a pericyclic rearrangement[114].

In radical chemistry[115] attention might be drawn to the following: a novel intramolecular radical hydroacylation of alkenes mediated by *tert*-dodecyl mercaptan[116]; an asym. radical 1,4-addition to β-benzoyloxy-α,β-ethylenecarboxylic acid amides (with $Mg(ClO_4)_2$ as Lewis acid and a chiral bis(Δ^2-oxazoline) as ligand), serving as an alternative to asym. aldol condensation[117]; a new carbonylative synthesis of α-methylene-carboxylic acid amides from acetylene derivs. involving initial radical