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π Shielding in organic synthesis

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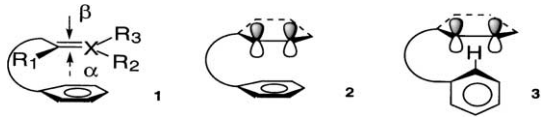
1. Introduction

The intent of this report is to highlight the various roles that π shielding effects play in contemporary organic synthesis. Herein, the term π shielding is used to signify that one face of an unsaturated moiety is shielded from attack of an incoming species by an interaction with a pendant aryl group, e.g. shielding of the α face on **1**. The exposed face is then subjected to regioselective additions, which may also impart a stereoselective component. The nature of the interaction between the unsaturated group and the aryl may either be of steric origin, merely serving to buttress against approach to the shielded face, or of electronic origin, wherein a stabilizing interaction between the two components is established. When the intramolecular distance between the two entities is within the 3–4 Å range, both categories of interactions are often commonly referred to as π stacking, regardless of whether a stabilizing interaction exists. Within this report we will refer to π stacking in cases where a positive attractive interaction between the components is implied, invariably where the π cloud of the unsaturated entity has either a face-to-face (**2**) or face-to-edge (**3**) relationship with the aryl. An earlier review summarizes these effects in asymmetric synthesis prior to 1995[1] and related accounts and discusses in more depth the nature of the π–π interactions.[2]



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2. Theoretical and spectroscopic analysis

Though the material for this report is derived from the organic synthesis literature over the period 1995–2001, a discussion of relevant theoretical treatise on the origins of π–π interactions is appropriate. One of the best studied

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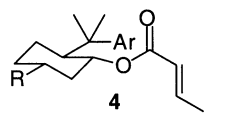
systems in this regard has been the 8-phenylmenthol chiral auxiliary originally developed by the Corey group in the 1970's.[3,4] Acrylate esters of this and related auxiliaries show pronounced diastereoselectivity in intermolecular addition, and the nature of the vinyl–aryl interaction has been scrutinized.[5] Recent semi-empirical studies of crotonates **4** supported the contribution of π stacking to diastereoselectivity, and suggested electrostatic forces were responsible for the interaction.[6] The nature of the interaction [face–face] was supported by an independent study and crystallographic analysis of **4**, R=H, which revealed a coplanar relationship between the aryl and acrylate groups.[7] These data blend well with earlier fluorescence quenching studies, which suggested a through space π–π interaction.[5]



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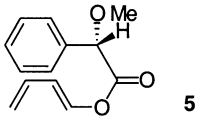

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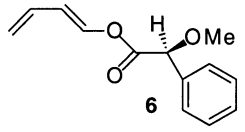

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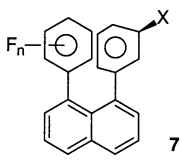
Theoretical studies have also been conducted on butadienyl esters of the *O*-methylmandelate chiral auxiliary introduced by Trost. The original hypothesis proposed face-to-face stacking as in **5**, however in depth analysis reveals that a more likely explanation for the effectiveness of this auxiliary involves the aryl adopting a perpendicular relationship with respect to the diene, as in **6**, i.e. a π-shielding rather than π-stacking phenomenon.[6,8,9] The need for accurate interpretation of the propensity for π–π interactions to develop has prompted numerous subsequent theoretical studies, including those involving aryl–aryl interactions. Cozzi and Siegel performed a comprehensive analysis on a series of 1,8-diarylnaphthalenes, and studied the variance of $\Delta G^{\neq}$ for aryl rotation as a function of donor/acceptor ability, e.g. **7**. The results clearly suggest that in this series, polar/electrostatic effects dominate over charge-transfer interactions.[10]



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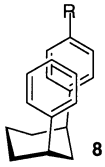

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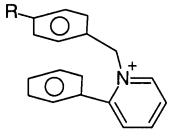

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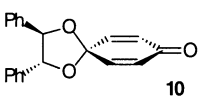
While *peri*-disubstituted substrates **7** reduce the possibility of face–edge interactions, a similar study on *cis*-1,3-diarylcyclohexanes revealed energy minima for both face-to-face (**8**) and edge-to-face orientation.[11] As previously, arene–arene electrostatic interactions were shown to predominate over charge-transfer interactions.[11] Another key study involved derivatives of *N*-benzyl-2-phenylpyridinium ion **9**, which suggested that a face-to-face, center-to-edge [FFCE] orientation was preferred over the alternate (splayed) conformation.[12] These and other examples serve to illustrate that the simple notion of π–π stabilization based on donor–acceptor interactions is often misleading, and that the true nature of the interaction(s) probably involves a combination of π–π and π–σ effects.[2]

One of the expected consequences of π–π interactions is that C–H bonds on the unsaturated entity will display characteristic shielding effects in their ^{1}H NMR spectra. Indeed, this has even been advocated as a diagnostic marker to screen various chiral auxiliaries for propensity to engage in π-stacking.[7] A recent study of chiral benzoquinone monoketals underscored the magnitude of these effects. Monoketals **11** and **12** were designed to facilitate vinyl–aryl shielding based on analysis of their C_2-symmetric parent **10**.



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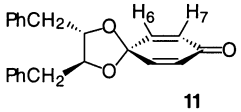

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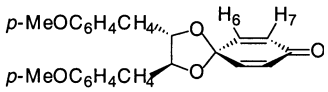

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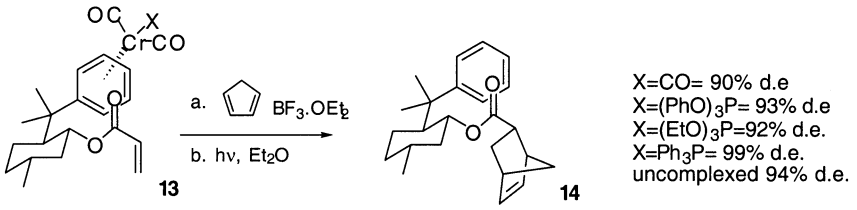
^{1}H NMR analysis of protons H6 and H7 confirmed this hypothesis, with H6 displaced upfield 0.49 and 0.51 ppm, respectively in **11** and **12**, and even H7 is displaced 0.21 and 0.20 ppm, respectively (relative to **9**).[13] Thus, a combination of ^{1}H NMR, X-ray crystallography, and fluorescence quenching studies can provide valuable insight to the origins of anticipated π–π attractive and π-shielding interactions. Such findings will also serve to validate ab initio studies on the origin of π–π interactions. Given the advances in computational capacity it is thus realistic to expect that such calculations will become a routine predictive tool for the design of new π–π interactive systems, in addition to its current use explaining the origin of such effects.

3. Asymmetric transformations

Given the nature of the pioneering reports of π–π interactive effects in organic synthesis,[4] it is perhaps unsurprising that the majority of investigators citing π shielding and π-stacking effects are in the area of asymmetric induction. The Section 3.1 is grouped according to reaction type but as will be gleaned, numerous other as yet unaddressed possibilities exist for the systems described.

3.1. Cycloadditions

3.1.1. Diels–Alder reactions. Since its introduction in 1975, the 8-phenylmenthol chiral auxiliary has been used to mediate a plethora of asymmetric transformations, one of the most popular being Diels–Alder cycloaddition to its vinyl esters.[3] The observed asymmetric induction to acrylate derivatives is believed to benefit from π–π interactions between the arene moiety and the enoate, which influences rotamer populations and contributes to the high (>90%) diastereoselection for addition of cyclopentadiene. In order to study the nature of the aryl–vinyl interaction, Jones and Chapman prepared a series of η6 chromium carbonyl complexes **13**, with varying degrees of propensity for backbonding to the arene.[14] Cycloaddition diastereoselectivity showed a clear correlation with donor ability of the arene, pointing to electronic effects that can be

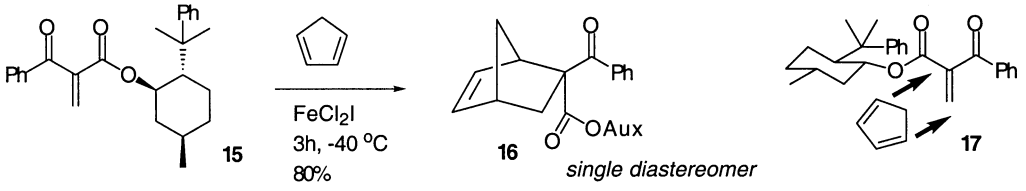


Scheme 1.

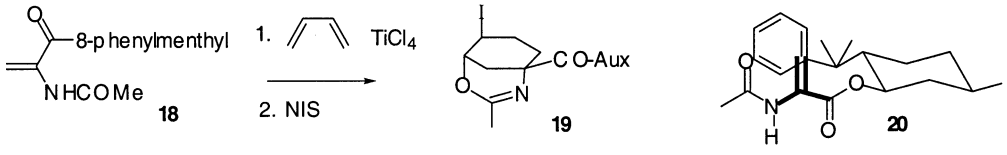
modulated by tuning the π donor ability of the arene (Scheme 1).[14] Though X-ray diffraction of **13** (X=CO) revealed an off center stacked face–face geometry, the data imply that electrostatic effects contribute strongly, since this particular derivative would be expected to disfavor any charge-transfer mode.[15] Implicit in this, and related systems (vide infra) is that π–π interactions can influence enoate geometry (*s-cis* versus *s-trans*) by providing some form of stabilizing interaction. A similar approach was used to investigate selectivity for the addition to acrylate derivatives of the benzyl oxazolidinone chiral auxiliary.[16] Yamaguchi and co-workers have extended the versatility of the 8-phenylmenthol auxiliary with cycloadditions to 2-methylene-1,3-dicarbonyl derivatives.[17] Notably, addition of cyclopentadiene to dienophile **15** proceeded with near total control, giving adduct **16** as a single isomer. Though the contribution of the phenylketone moiety was not delineated, approach of the diene as indicated in **17** was presumed, the lower face of the methylene effectively shielded by the aryl group of the auxiliary.[17] Of additional interest, selectivity even at room temperature was still excellent, with a >99:1 ratio of adducts (Scheme 2).

Application has also been made with cycloaddition to acetamidoacrylates derived from 8-phenylmenthol. Titanium catalyzed addition of butadiene to **18** gave >99:1 of the cycloadduct with (*S*) stereochemistry at the new stereocenter, which was converted to bicyclo [3.3.1] derivative **19** on treatment with *N*-iodosuccinamide (Scheme 3).[18] A model was proposed involving addition to the *si* face of the enamide, viz. **20**.[18] In a related effort, Cativiela et al. have demonstrated moderate selectivity in cycloaddition to enamides derived from 1-amino-2-phenyl-1-cyclohexanecarboxylic acid, e.g. **21**.[19] *endo* Cyloadduct **22** was formed in good yield, and diastereocontrol rationalized in terms of π shielding of the *re* face of the enamide, as shown in **23** (Scheme 4). The authors have developed routes to all four diastereomers of **21**, and further modifications and enhancements would seem possible. The importance of the stereoselective Diels–Alder reaction has led to the development of a variety of other auxiliaries, many of which impart the features of π facial selectivity first exploited in the cyclohexyl based systems. Carreno and Ruano have reported diastereoselective cycloadditions to chiral toluenesulfinyl benzoquinones, e.g. **24** (Scheme 5).[20]

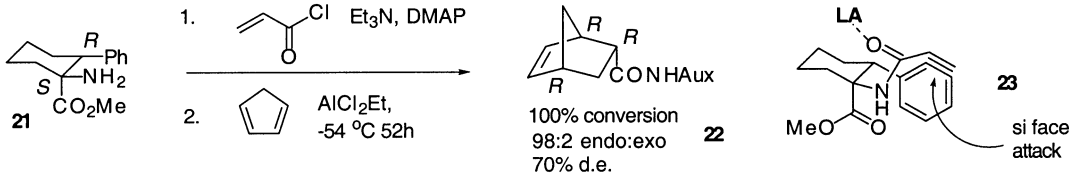
Cycloadduct **25** was obtained as a single diastereomer, and the working model used to explain facial selectivity invokes steric approach control to the underside as in **26**. This arrangement is established by shielding the upper face by



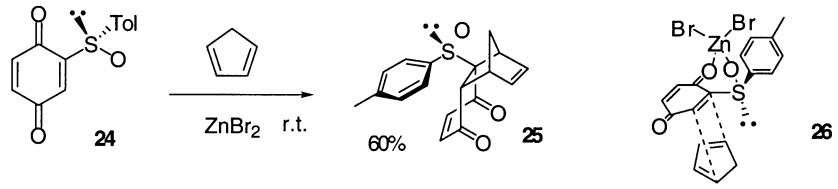
Scheme 2.



Scheme 3.



Scheme 4.



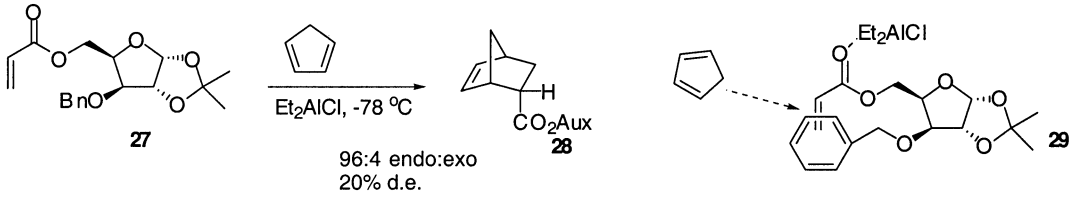
Scheme 5.

chelation of the sulfoxide to Lewis acid, and is augmented by the tolyl group.[20] Carbohydrate derivatives are another potentially rich source of chiral auxiliaries, and Ferreira's group have recently reported on a series of α-D-xylofuranose derivatives.[21] Though acrylate ester **27** undergoes *endo* selective cycloaddition to give **28**, diastereoselectivity is low (Scheme 6). The rationale behind this family of auxiliary is that π stacking of the acrylate with the pendant benzyl group should shield the upper face to attack, i.e. **29**. However, the flexibility of both the benzyl and acrylate groups probably reduce the likelihood of a stacked rotamer population, thus contributing to low ee.[21]

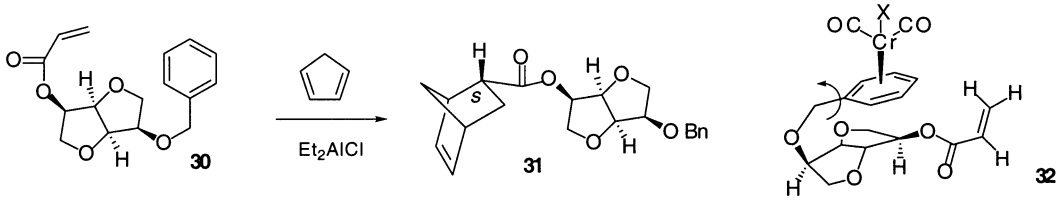
Such flexibility is reduced in the isomannide derived acrylate **30**, which however undergoes highly *endo* and diastereoselective cycloadditions, e.g. **31**, which is formed in 90% de (Scheme 7). Spectroscopic analysis suggests that the benzyl group shields one face of the acrylate ester, and this effect can be further amplified by complexation of the arene ring as in **32**, which results in the increase in de to >95%.[22]

3.1.2. Catalytic Diels–Alder reactions. Catalytic variants of the above have been much sought after, and research in this field was spurred by a series of catalysts developed in the Corey group which were designed to foster catalyst–substrate π–π attractive interactions.[23,24] The Engberts group have recently succeeded in developing conditions for a water based catalyst, which allows conversion of pyridyl enone **33** into adduct **35** using a catalyst derived from abrine **34** and copper II species (Scheme 8).[25] The authors suggest that the indolyl subunit effectively shields one face of the (coordinated) dieneophile, directing the incoming diene to the underside of the complex **36**.[25] A face selective Diels–Alder catalyst was also reported by Jones and Guzel. The active species, an aluminum metallocycle **37** derived from naphthalene-1,2-diol is highly *exo* selective, and produces cycloadducts, e.g. **38**, in high ee (Scheme 9).[26] Selectivity was rationalized on the basis of *re* face attack to the coordinated enal, the geometry of which is enforced by the bulky arene complex as shown in **39**.[26]

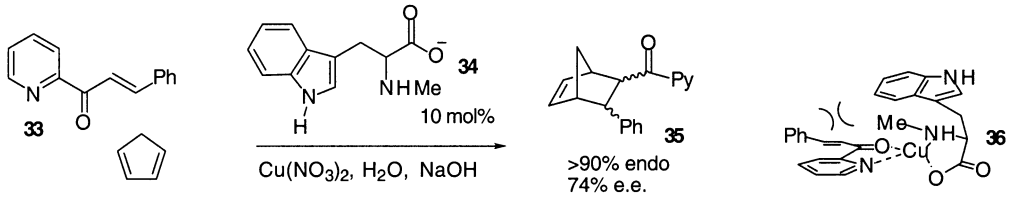
3.1.3. Hetero Diels–Alder reactions. Kibayashi has employed a naphthylmenthyl auxiliary to achieve highly diastereoselective cycloadditions to the derived acylnitroso dienophile **40** (Scheme 10).[27,28] Adduct **41**, which could be produced with up to 14:1 selectivity, suggested a transition



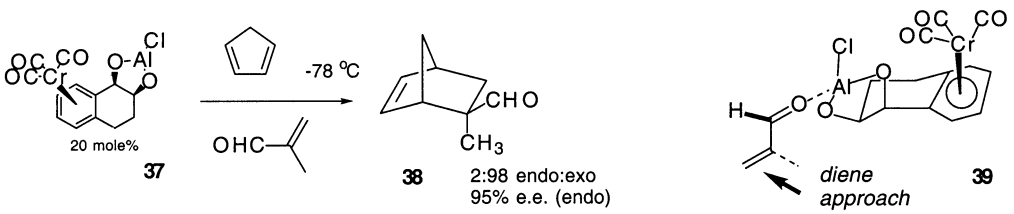
Scheme 6.



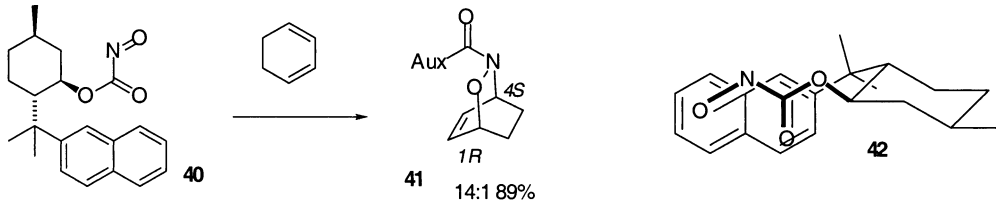
Scheme 7.



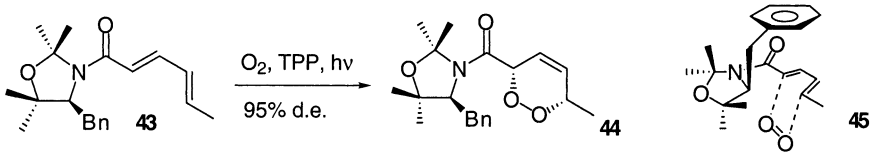
Scheme 8.



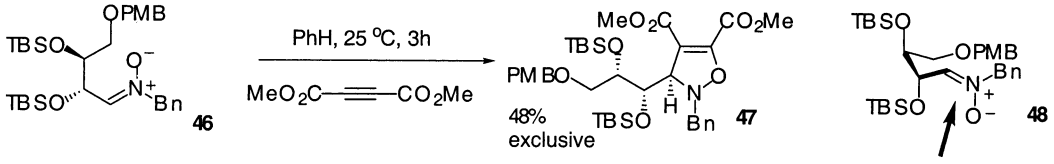
Scheme 9.



Scheme 10.



Scheme 11.

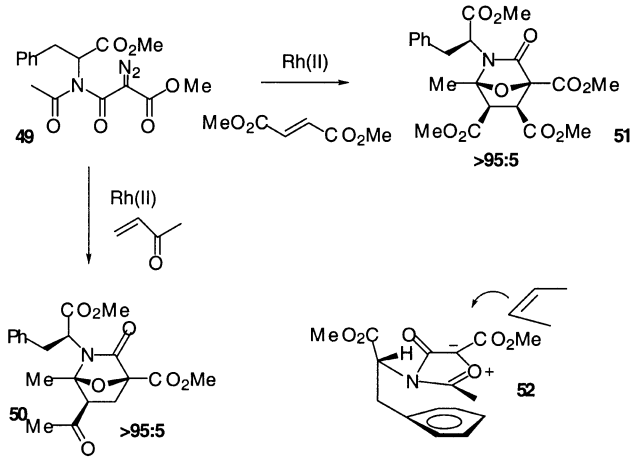


Scheme 12.

state as shown in **42** where the naphthyl group enforces an *s-cis* orientation of the acylnitroso group via positive interactions. Analogous methodology was then used by the authors in an asymmetric total synthesis of the alkaloid (−)-Epibatidine.[28]

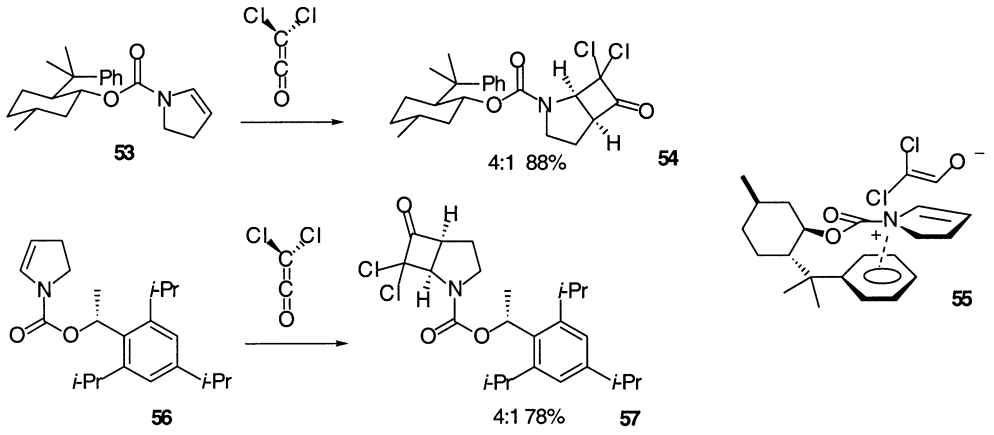
Wirth et al. have reported highly selective [4+2] cycloadditions of singlet O_2 to 2,2-dimethyloxazolidine **43**.[29] The de of adduct **44** is high and the model used to explain selectivity is consistent with observed data, indicating a unique interaction between the *s-cis* diene and the benzyl substituent (**45**) forcing *lk* attack to give the observed endoperoxide adduct (Scheme 11).[29]

3.1.4. [3+2] Cycloadditions. Saito et al. have utilized the concept of facial shielding for the design of chiral nitrones used for stereoselective [3+2] cycloadditions. In one example, dipole **46** underwent cycloaddition with DMAD to give adduct **47** exclusively.[30] This is rationalized on the basis of exclusive shielding of one C=N face of the dipole, presumably achieved by synergy of the *p*-methoxybenzyl and *N*-benzyl groups, viz. **48** (Scheme 12).[30] Padwa reported a series of [3+2] cycloadditions of isomunchnone dipoles derived from α-diazoimides. Very high levels of facial preference were attained, giving access to a wide range of potential products viz. **49→50/51**.[31] The rationale behind this selectivity was effective π-shielding of one face of the dipole by the benzyl group, which in turn promotes the observed *syn* selectivity for addition, i.e. **52** (Scheme 13).[31]



Scheme 13.

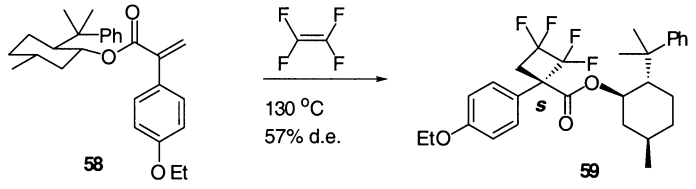
3.1.5. [2+2] Cycloadditions. Chiral auxiliary mediated [2+2] cycloadditions have proven effective, both in terms



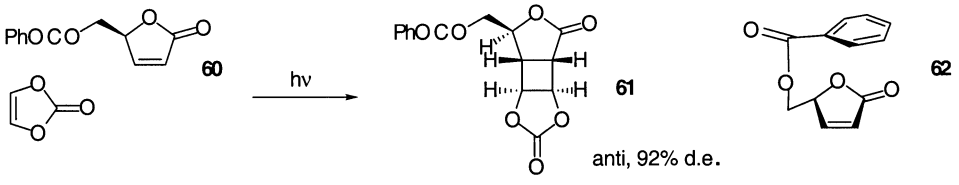
Scheme 14.

of efficiency and selectivity. Correia recently reported the addition of dichloroketene to phenylmenthol derived enamide **53**. Product **54** was formed with reasonable stereocontrol, and subsequently used in a synthesis of the (−)-Geissman–Waiss lactone.[32] The authors attribute facial control on the basis of **55**, the pseudoenolate approaching the *si* face of the enamide since the *re* face is precluded by π shielding with the aryl group (Scheme 14). Interestingly, both *sp* and *ap* conformations (enamine) were equally populated at room temperature, implying that the *sp* form may foster a unique interaction to develop with the incoming substrate.[32] Similarly, enamide **56** gave 2+2 adduct **57**, albeit with reduced efficiency.[32] [2+2] Cycloaddition of tetrafluoroethylene with 8-phenylmenthol enoate **58** has been reported, giving product **59** in moderate selectivity (under these optimal conditions yield is reduced to only 70%, Scheme 15).[33] The phenylmenthol auxiliary proved more effective than both its naphthyl analog, a phenyl cyclohexyl derivative and a norephedrine derived system. The rationale for its selectivity involved π shielding of the *re* face of the *s-cis* enoate, forcing cycloaddition to proceed from the exposed *si* face.[33]

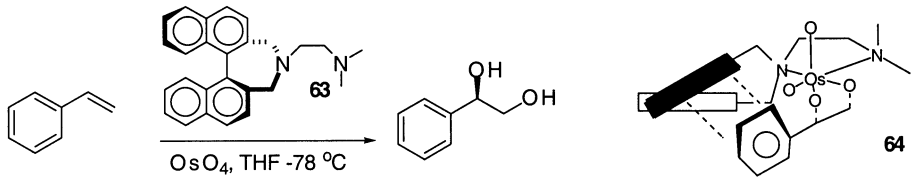
Photocycloaddition of vinylene carbonate with furanone **60** has been reported (Scheme 16).[34] Product **61** is formed in high de, and control experiments revealed that the phenyl ester plays a key contribution to stereocontrol. The authors envisage that the aryl group shields one face of the carbonate in **62** promoting addition to the *anti* face; additional flash photolysis studies were conducted and supported the hypothesis that the reaction proceeds through a biradical intermediate.[34]



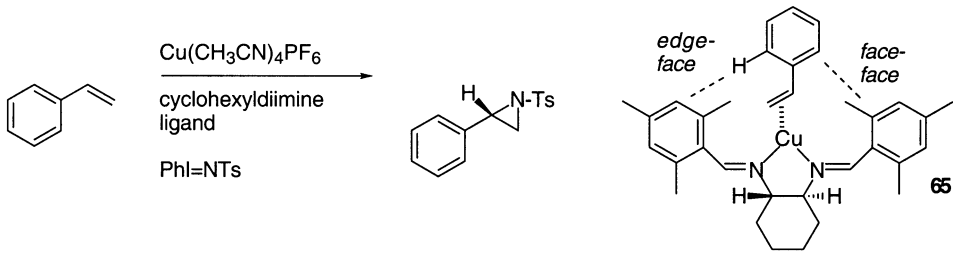
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

3.1.6. Other cycloadditions. Rosini and Salvadori have studied the asymmetric dihydroxylation of styrenes with optically active diamines such as **63** (Scheme 17).[35] Styrene itself is converted to the corresponding *R* diol in 83% yield and 96% ee. Though the process also works well for stilbene (98% ee), a range of other styrenes gave only moderate enantiocontrol, prompting the authors to advance a working model to explain selectivity. This is reasoned to involve (in the case of stilbene) a favorable π–π interaction between the substrate and naphthyl group, exposing the *si* face to dihydroxylation and shielding of the *re* face, viz. **64**.[35]

Jacobsen has proposed a working model to explain the origin of enantioselectivity for aziridination and cyclopropanation using copper complexed C_2-symmetric 1,2-diamine catalysts. In the case of styryl substrates, the model identifies both face–edge and face–face π–π interactions between the substrate aryl and catalyst aryl groups, viz. **65** (Scheme 18).[36,37] The model is supported by X-ray data, and by both conventional and solid-phase MAS NMR analysis.[38]

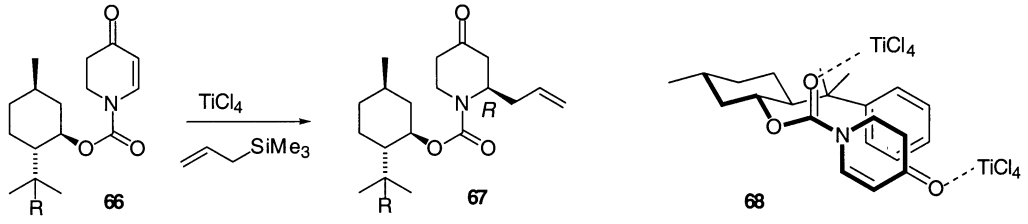
Table 1. $TiCl_4$ Promoted conjugate allylation of 8-arylmenthol derived *N*-acyl enamininones

Entry	R	Ratio *R*/*S*	Yield
1	H	1.1:1	96
2	Ph	11.7:1	97
3	*m*-$MeOC_6H_4$	17.4:1	90
4	*p*-$MeOC_6H_4$	17.1:1	92
5	*p*-BrC_6H_4	8.1:1	90
6	*p*-$NO_2C_6H_4$	12.6:1	86
7	2-Naphthyl	30:1	89
8	Cyclohexyl	1.2:1	76

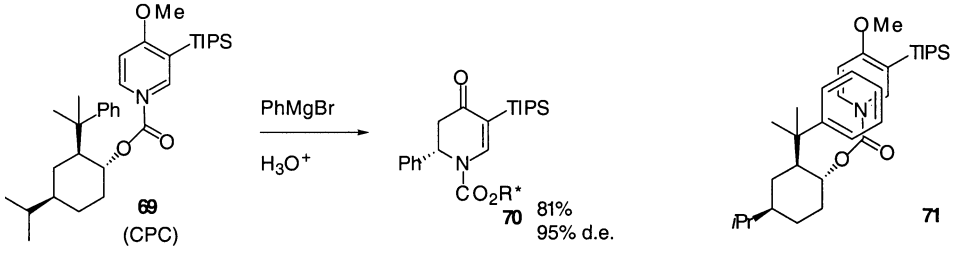
3.2. Conjugate additions

The success of the 8-phenylmenthol auxiliary has prompted numerous investigations which capitalize on the inherent design principle—i.e. stereoselective additions to derivatives which can benefit from π shielding afforded by the aryl group of the auxiliary. Kibayashi has performed a comprehensive screen of 8-phenylmenthol analogs for the conjugate allylation of *N*-acyl-2,3-dihydro-4-pyridones derivatives **66**.[39] Products **67** were formed in high yield, but as expected selectivity was greatly influenced by the nature of the substituent R (Table 1). Optimal selectivity was attained with the 2-naphthyl derivative, and the hypothesis for selectivity, supported by control experiments, involves allylation to the *s-trans* form of the doubly chelated enecarbamate **68** (Scheme 19).[39]

In independent studies, Comins (who first demonstrated the utility of 2,3-dihydropyridones in asymmetric synthesis)[40] conducted a thorough survey of cyclohexyl based auxiliaries for asymmetric addition to derived acylpyridinium ions. The most effective of these proved to be an isopropyl derivative (CPC) of an α-cumyl cyclohexanol introduced earlier.[41] Addition of aryl Grignard to **69**



Scheme 19.



Scheme 20.

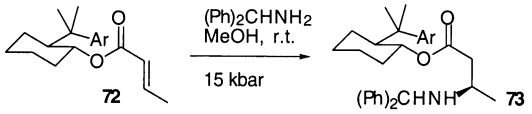
Table 2.

Ar	% de
Ph	60
o-$CH_3OC_6H_4$	>99
p-C_6H_5O–C_6H_4	97
2-Naphthyl	98

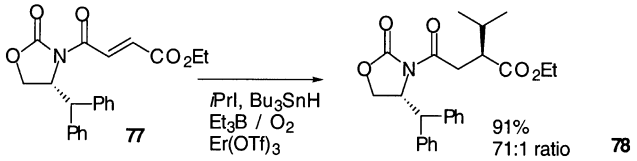
proceeds with very high selectivity, giving access to dihydropyridone building block **70** on hydrolysis (Scheme 20).[41] Overlap of the aryl group with the pyridinium ion is reasonably assumed to be a contributing factor (**71**) to the high selectivity observed. The positive contribution of the isopropyl group is less easily explained, but could potentially influence rotamer populations, which in turn establish optimal overlap for the π–π interaction.[41]

Dumas and D'Angelo also reported a comparative study of various cyclohexyl auxiliaries directed towards diastereoselective amination of acrylates.[42] For derivatives **72**, aryloxy substituted auxiliaries were optimal, giving very high selectivity for product **73** in one case (Table 2). Solution phase VT NMR studies on acrylates **72** revealed characteristic π shielding effects for the vinyl hydrogens which became pronounced on cooling, suggesting population of the *s-trans* conformer (Scheme 21).[42]

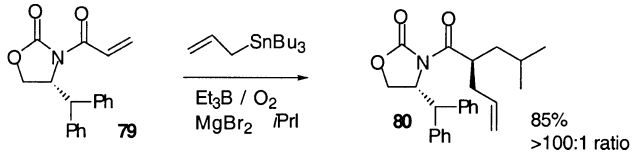
Sibi has demonstrated the effectiveness of the 4-diphenyl-



Scheme 21.

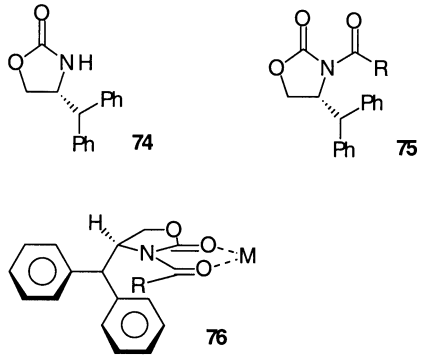


Scheme 22.



Scheme 23.

methyl-2-oxazolidinone auxiliary **74** in a series of investigations.[43] Acyl derivatives **75** and their enolates undergo a variety of highly selective additions by virtue of the dominant influence of the diaryl group, which, when the dicarbonyl groups are chelated to appropriate Lewis acid as in **76**, direct incoming reagents to the upper face.

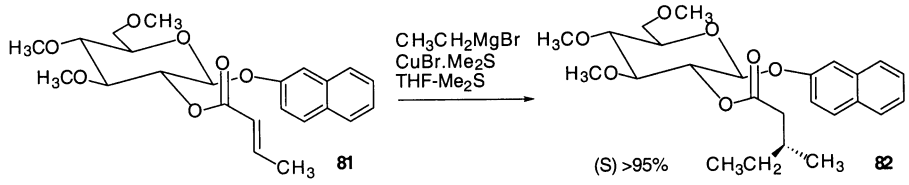


Depending on the nature of the appendage R, the possibility for additional π–π and π-shielding effects exists, and have been carefully investigated.[43] One of the most spectacular findings was the highly selective conjugate alkylation of vinyl ester **77**, giving product **78** with a 71:1 ratio (Scheme 22).[44]

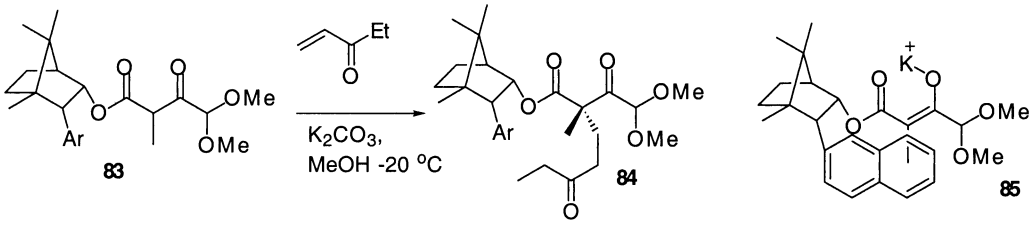
Another elegant application is the tandem alkylation–allylation sequence performed on **79**, giving the substituted product **80** with essentially complete stereocontrol (Scheme 23).[45] The availability of **74** from serine methyl ester, coupled with the range of indicated applications suggest this auxiliary will likely become widely used.

Chiappe et al. have developed a naphthyl derivative of a glucopyranoside as an auxiliary for conjugate addition.[46] Borrowing on the established trends in analogous naphthyl-cyclohexyl based auxiliaries, acrylate ester **81** undergoes selective alkylation to yield diastereomer **82** with (*S*)-chirality at the new stereocenter (Scheme 24).[46] Implicit in the design of this auxiliary was the likelihood of positive interactions between the vinyl and naphthyl groups, serving to lock in the *s-trans*, *syn* conformation of the acrylate, and shield the lower face from nucleophilic attack.

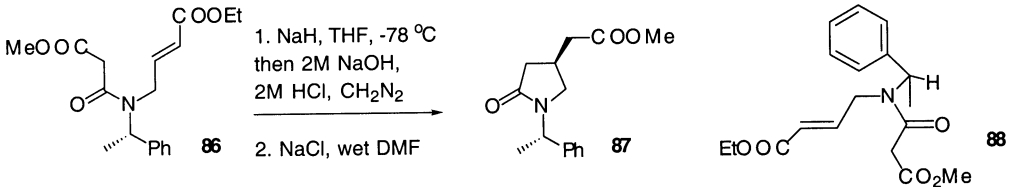
During a synthesis of the trisporic acid family of fungal pheromones, Ruveda et al. required diastereoselective addition of the enolate derived from β ketoester **83** to ethyl vinyl ketone.[47] The product **84** was formed in good yield, and the diastereoselectivity afforded was explained on the basis of the naphthyl group engaging in shielding of one face of the potassium enolate **85** (Scheme 25). A range of other auxiliaries capable of fostering a β shielding interaction were examined, but bornyl **83** proved the most effective.[47]



Scheme 24.



Scheme 25.



Scheme 26.

Orena has reported a route to enantiomerically pure pyrrolodineacetic acids which employs a diastereoselective intramolecular conjugate addition as a key step.[48] The enolate derived from **86** cyclizes to form pyrrolidin-2-one **87** following decarboxylation (Scheme 26). Though the diastereomeric ratio is only 8:2, separation of the major product **87** was possible. Selectivity is presumed to be a function of π shielding of one face of the enolate by the phenyl group of **88**.[48]

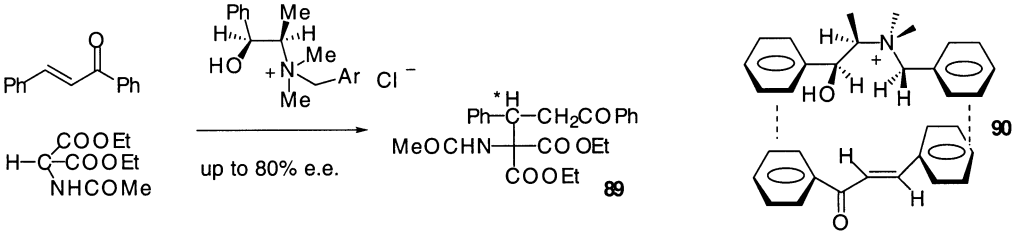
Conjugate addition of diethyl acetamido malonate to chalcone has been studied using various phase transfer catalysts. In one example, using an ephedrine derived benzalkylammonium salt, up to 80% ee of product **89** was obtained.[49] The rationale behind this high selectivity is a π–π interaction between the catalyst and chalcone substrate, as indicated in **90** (Scheme 27).[49]

An unprecedented and highly selective conjugate addition of β-ketosulfoxide **91** with substituted benzylidene malononitriles has been reported.[50–52] In the case of **92**, product 4*H*-pyran **93** is formed exclusively and in high yield (Scheme 28). The working model to explain this selectivity involves favorable π–π interactions of the pyridine and haloarenes, augmented by bridged hydrogen bonds (**94**).[50]

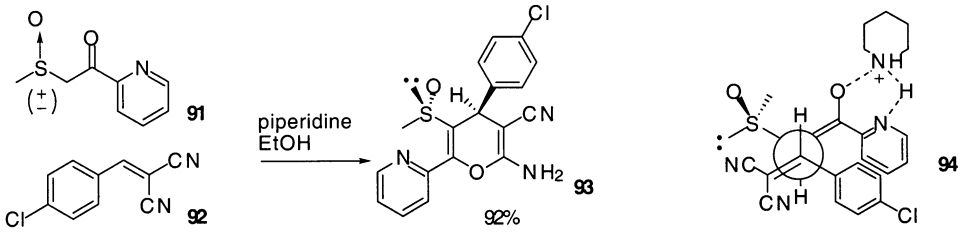
Finally, a completely diastereoselective Michael-aldol process has been reported. Enone **95** is converted directly to tricyclic product **96** in the presence of TMS-I and hexamethyldisilazine[53] The 8-phenylmenthol auxiliary was selected due to favorable π–π interactions which would shield one face of the enone to attack from the TMS enol ether (Scheme 29).[53]

3.3. Alkylations

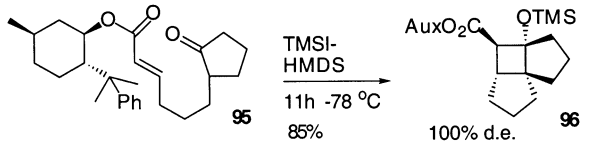
As noted above, the 4-diphenylmethyl-2-oxazolidinone auxiliary is highly effective, and as expected alkylations



Scheme 27.



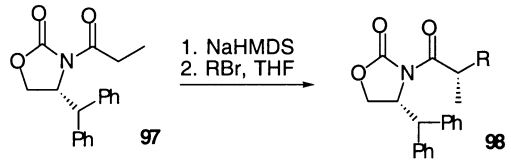
Scheme 28.



Scheme 29.

Table 3.

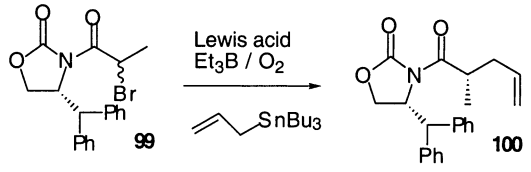
R	% de
$PhCH_2$	>98
$tBuOCOCH_2$	>99
C_3H_5	>99



Scheme 30.

Table 4.

LA	Ratio
None	1:1.8
$BF_3{\cdot}OEt_2$	1:1.4
$MgBr_2$	>100:1
$Yb(OTf)_3$	5:1
$Sc(OTf)_3$	>100:1



Scheme 31.

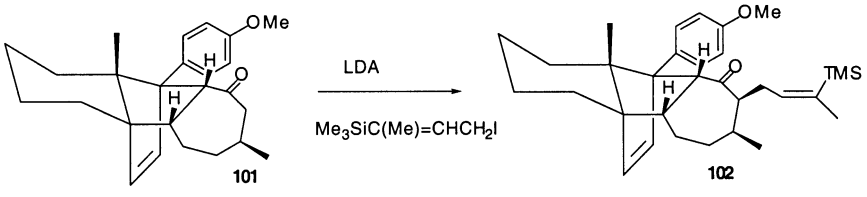
of alkanamide derivatives proceeds smoothly. In the case of **97** alkyl and benzyl halides alike give excellent product de's **98**, Table 3 (Scheme 30).[54] Additionally, Sibi has demonstrated allylation of α-haloderivatives **99** also proceeds with excellent selectivity.[55] A range of Lewis acids were surveyed (Table 4) leading to optimization for formation of **100**, a versatile building block for asymmetric synthesis (Scheme 31).[55]

An intriguing example of diastereoselective alkylation involving π shielding was reported by Winterfeldt et al. as part of a synthesis of (+)-clavularin A.[56] The enolate of **101** underwent clean alkylation to give **102** (Scheme 32). Though remote, π shielding of the enolate by the pendant aryl group was invoked to explain the high *syn* stereochemistry observed, although the role of the alkoxy group was not delineated.[56]

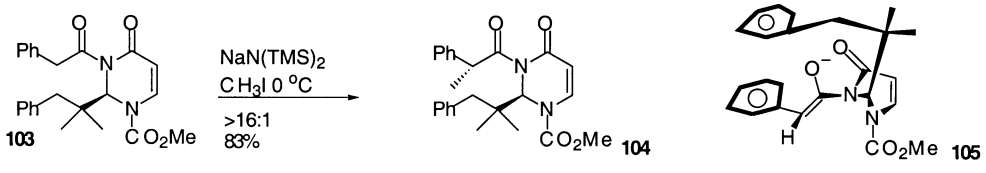
Negrete et al. have studied the diastereoselective alkylation of enolates derived from a range of popular auxilaries.[57] In an effort to scrutinize the influence of intramolecular π–π interactions, the sodium enolate of a range of aryl pyrimidinones including **103** were studied. In this case methylated product **104** is produced with appreciable facial selectivity and high conversion (Scheme 33). Clearly this type of auxiliary (produced from asparagine) is effective in the π shielding of one face of the enolate (**105**) and additional applications would seem attractive.[57]

In an investigation of hippurate alkylation, McIntosh et al. found that the benzylation of naphthyl cyclohexane **106** was most selective, the corresponding phenylmenthyl analogs giving only 85% de.[58] The selectivity observed for the formation of **107** was attributed to π–π interactions which in turn established an *anti-gauche* orientation for the enolate dianion (Scheme 34).[58]

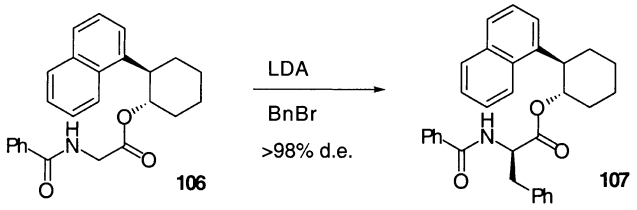
Berkowitz has conducted a thorough study of the asymmetric alkylation of vinyl glycine derived dianions, using various cyclohexyl auxiliaries.[59] For substrates **108**, optimal selectivity was obtained with Ar=2-naphthyl, and the origins of selectivity were probed using semi empirical methods. The results of this study suggest a favorable rotamer population involving face–face vinyl–aryl π–π



Scheme 32.



Scheme 33.



Scheme 34.

interactions of an electrostatic nature. This could involve the '*exo*-extended' arrangement as shown in **110**, which would promote *si* face alkylation to give **109** (Scheme 35).[59]

Diastereoselective allylation of imines derived from (*S*)-phenethanamine have been reported by Savoia.[60] In the case of aromatic aldimines, e.g. **111**, the high levels of induction observed were attributed to *re* face attack, promoted by a transition state were the two aryl groups adopt a quasi parallel orientation, which reduces unfavorable steric interactions and possibly promotes a π-stacking interaction, viz. **113** (Scheme 36).[60]

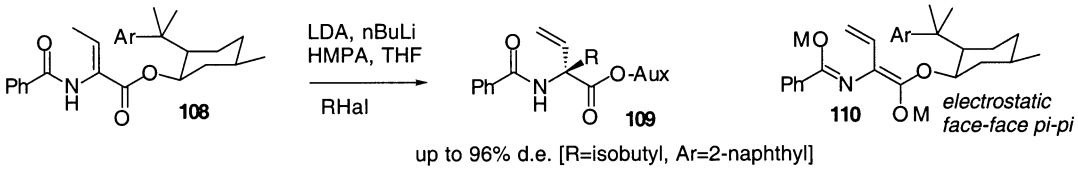
Finally, a study on the double alkylation of acetophenone has been made using phase-transfer conditions.[61] In the formation of **114**, a blend of chemical, theoretical and kinetic studies suggested that a developing edge–face π–π interaction developed in the transitions state **115**, and this has a direct impact on product distribuition (Scheme 37).[61]

3.4. Carbocyclizations

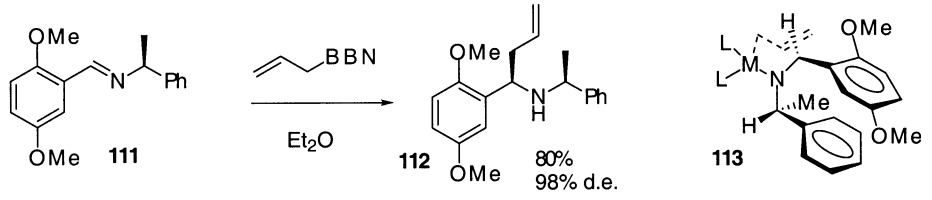
A series of asymmetric radical cyclizations were investigated by Tsai et al. involving a range of chiral auxiliaries.[62] Under optimal conditions, 8-phenylmenthol derived sulfide **116** underwent 5-*exo*-trig cyclization to give **117** with moderate diastereoselectivity. Commenting on the lower selectivity obtained with other auxiliaries [including menthol and camphor based systems], the authors suggest that the aryl group of **116** effectively shields the *si* face of the incipient radical center in (viz. **118**), leading to *re* face attack (Scheme 38).[62] Naphthyl derivatives were not examined, and it is tempting to speculate that yet further increases in de may be attainable.

Comins has harnessed the stereodirective capacity of the 8-phenylmenthol auxiliary in an asymmetric Pictet–Spengler reaction. Carbamate **119** underwent condensation to **120** in good (68%) yield, and reductive removal of the auxiliary led to (−)-laudanosine in 63% ee (Scheme 39). Similar protocols, using the trans-2-(α-cumyl)cyclohexyl auxiliary were used for the asymmetric synthesis of (+)-glaucine and (−)-xylopinine. The rationale for the critical ring closure is reasoned to involve iminium ion **121**, which enjoys lower face shielding by the phenyl group of the auxiliary, and possibly an electrostatic interaction.[63]

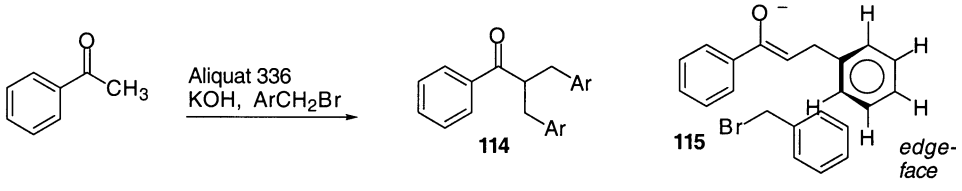
Tietze and Schunke employed the Evans benzyl oxazolidinone auxiliary for a Sn catalyzed intramolecular cyclization involving an allylsilane.[64] Derivative **122** underwent efficient and diastereoselective closure to **123** (Scheme 40), and selectivity was explained on the basis that one face of



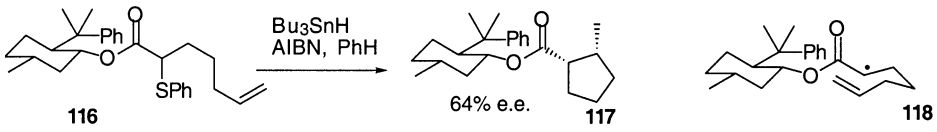
Scheme 35.



Scheme 36.



Scheme 37.



Scheme 38.

the allylsilane acceptor (alkylidene) was shielded by positive interaction with the benzyl group of the auxiliary.[64] Dulcere et al. have described an interesting radical carbocyclization sequence which might derive selectivity from some form of π shielding interaction.[65] Radical cyclization of **124** proceeds with good selectivity to give product **125** following 5-*exo-dig* attack and concomitant 1,6 hydrogen transfer and then cyclization (Scheme 41). Following semi empirical analysis, the authors proposed that selectivity is derived from a face-to-edge C–H to π interaction **126**, which favors formation of the *syn* product via the intermediate (though configurationally unstable) benzyl radical.[65]

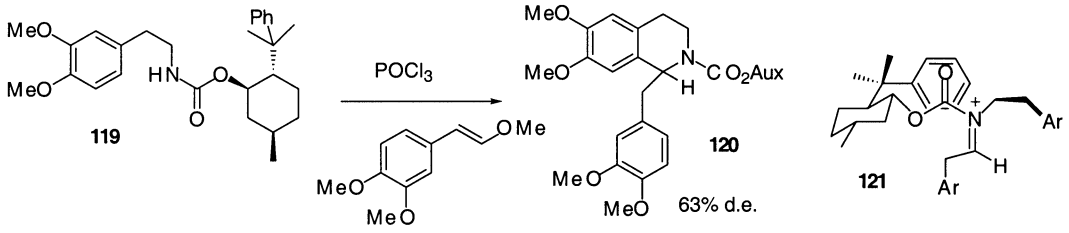
3.5. Aldol reactions

During a study on the synthesis of (+)-3-oxacarbocyclin, Gais et al. desired a diastereoselective aldol addition to **127** using an appropriate ester enolate. Both cyclohexyl and camphor based auxiliaries were screened, and the de for product formation **128** compared for enolates **129**–**131**.[66] As can be seen, though chemical conversion was best with the 8-phenylmenthol auxiliary, diastereoselectivity was high in each case, and rationalized on the basis of π shielding of one face of the lithium enolate by the pendant aryl group in the auxiliary (Scheme 42).[66]

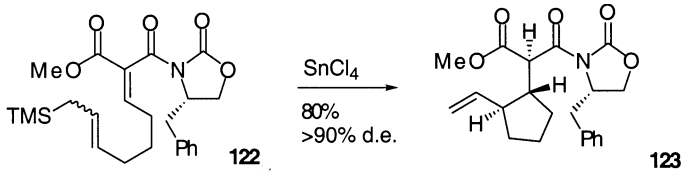
3.6. Other reactions

Dai has investigated stereoselective Wittig reactions under the influence of the 8-phenylmenthol auxiliary. Bromoester **132** coupled with phenylcyclohexanone to give enoate **133** in up to 80% de using the intermediate arsine salt. The influence of the phenyl group of the auxiliary was probed and a working model proposed involving enolate **134**, with its lower face shielded, engaging in an equatorial attack on the ketone (Scheme 43).[67]

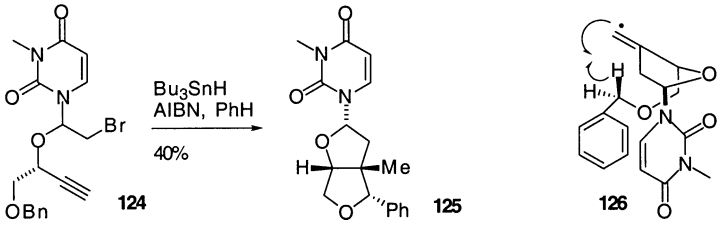
An asymmetric Darzens reaction has also been reported using building block **132**.[68,69] Product **135** was formed with high diastereoselectivity (Scheme 44), a consequence of the *si* face of the *z* enolate adding to the *si* face of the ketone as shown in **136**.[68,69]



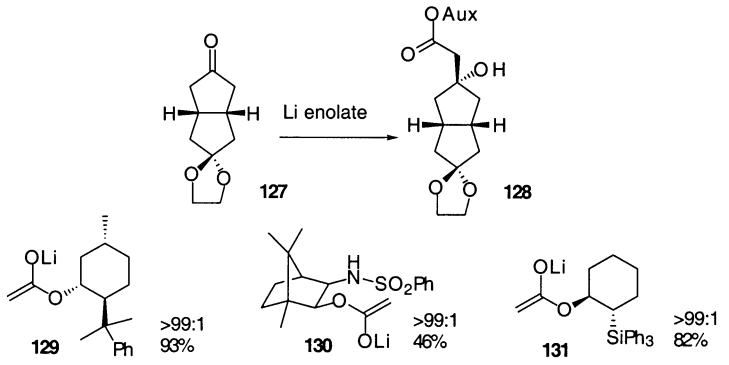
Scheme 39.



Scheme 40.



Scheme 41.

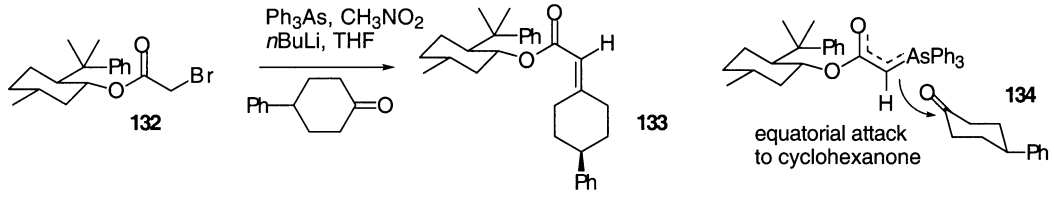


Scheme 42.

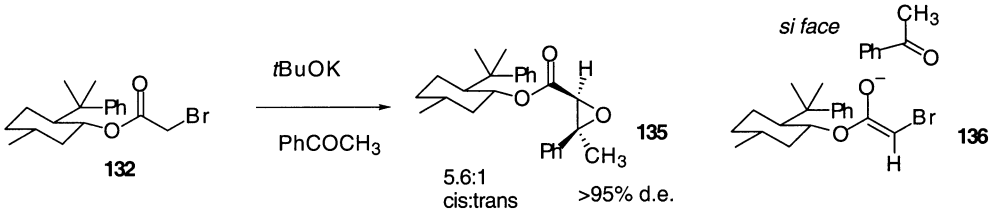
The Michael addition of achiral *N*-protected glycine esters to an 8-phenylmenthol derived Fischer alkenylcarbene has been examined.[70] Addition to **137** proceeded efficiently and with good diastereoselectivity. The authors propose that π shielding of one face of the Michael acceptor dictates approach of the anion as shown in **139** (Scheme 45). Products **138** were subsequently transformed to β-substituted glutamic acids.[70]

Rosini has studied the effectiveness of (*R*,*R*)-1,2-diphenylethane-1,2-diol as a chiral auxiliary for reduction of α-ketoesters.[71] Substrate **140** undergoes selectride reduction to give **141** with moderate selectivity. Diastereoselectivity was rationalized on the basis of **142**, where stacked aryls promote *re* face attack on the ketone. Addition of Lewis acid resulted in total loss of selectivity, presumed a consequence of carbonyl complexation disfavoring the orientation depicted in **142** (Scheme 46).[71]

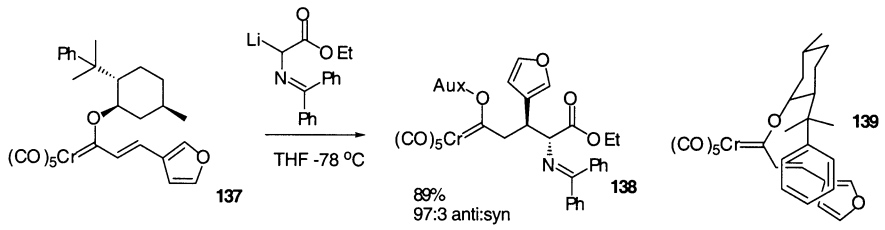
A study on the diastereoselective reduction of 2-substituted-2-carbomethoxy cyclopentanones was conducted, revealing that subtle interactions between the carbonyl π system and the 2-substituent can have a pronounced effect on stereocontrol.[72] In the case of **143**, the exclusive product from borohydride reduction is **144** (Scheme 47), rationalized on the basis of the allyl group establishing a π-stack with the ketone, effectively shielding this face from approach of the reductant (**145**). Addition of Lewis acid reversed the



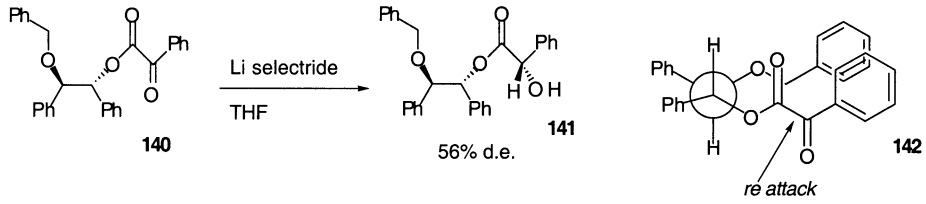
Scheme 43.



Scheme 44.

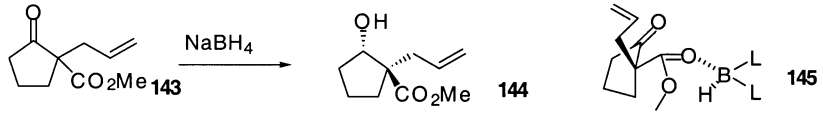


Scheme 45.



140 141 142

Scheme 46.



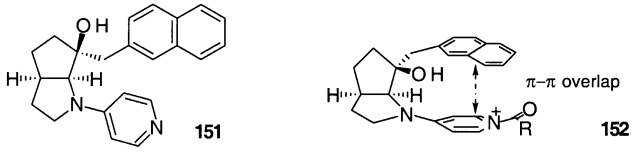
143 144 145

Scheme 47.

selectivity, presumably by chelation to the carbonyl thereby disfavoring the proposed vinyl–carbonyl π–π interaction.[72]

Trombini has studied the addition of 1,3 dipoles with furans.[73] In the case of **146**, addition of 2-trimethylsiloxy furan provides access to lactone **147**, via generation of an intermediate *N*-silyloxyiminium ion, 1,3 addition producing a γ substituted unsaturated γ lactone (91:9 ratio), which is then captured to form the tetrahydrofuro[2,3-*d*]isoxazol-5(2*H*)-one on treatment with silica gel (Scheme 48). For the critical 1,3 addition step, the authors propose that the furan nucleophile approaches the nitrone ion along a Burgi–Dunitz trajectory, offering its *si* face for attack on the *re* face of the nitrone **148**. The authors suggest that developing π–π stacking interactions between the substrates contribute to the stereochemical course of the addition.[73] Sato has studied the effect of different chiral auxiliaries on the asymmetric Bayliss–Hillman reaction.[74,75] The most effective substrate was **149**, undergoing addition of a low-valent titanium complex and subsequent addition to benzaldehyde to give **150** with extremely high selectivity (Scheme 49). Implicit to the stereocontrol is shielding of one face of the acetylene–titanium complex by the diphenylmethyl group.[74] Both phenyl cyclohexyl and phenylmenthol auxiliaries were inferior, suggesting the need for rigid shielding of the intermediate complex.

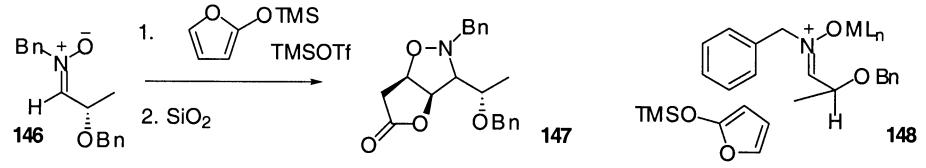
An interesting catalyst for the kinetic resolution of alcohols was introduced by Fuji. Ligand **151** functions as a nucleophilic catalyst for the asymmetric acylation of a variety of alcohols, with product ee's in excess of 99%, and selectivity factors (*s*) of over 10 using isobutyric anhydride as acyl donor.[76] The 2-naphthyl group plays an integral role in the induction process, and one possible orientation invoked by the authors involves π-shielding of the incipient acylpyridinium ion as shown in **152**.



151 152

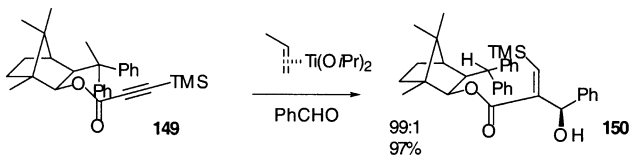
4. Artificial receptors

Though not defined by the same boundaries as those illustrated above, there is growing interest in the development of synthetic receptors where interaction of diaryl appendages (**153**) adopt an otherwise unexpected π–π oriented conformation to facilitate either recognition of an entity within the framework (**155**), or external to it (**154**).



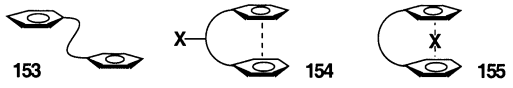
146 147 148

Scheme 48.



149 150

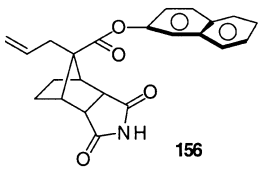
Scheme 49.

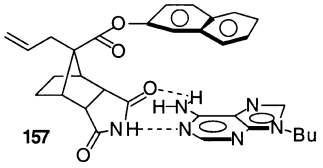


153 154 155

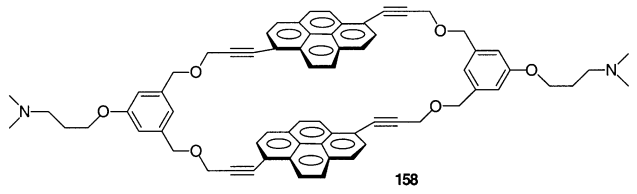
An example is the synthetic receptor **156** developed by Deslongchamps, which was designed as a probe for stacking interactions in A:T base pair mimics. The host guest

complex of this receptor with 9-butyladenine **157** was studied, and the participation of π stacking interactions confirmed by NMR analysis.[77]





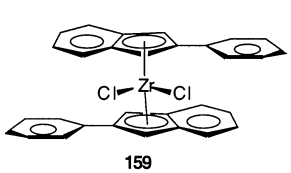
Rotello has developed a similar receptor for recognition of flavins.[78] A wide variety of molecular inclusion complexes of type **155** are also known, and the reader is referred to recent review articles.[79–82] A recent application from Inouye's laboratory lies in the design of neutral cyclophane-like cavities, e.g. **158**, designed as a host for arenes, including porphyrins.[83] Spectroscopic analysis revealed π-shielding of the pyrene protons in the NMR spectra, and excimer-emissions observed in the fluorescence spectra indicate proximal interaction of the pyrene groups.

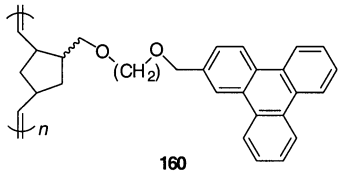


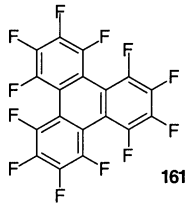
Another important application of systems of type **155** lies in chiral recognition, and separation of individual enantiomers, many of which have been applied in chiral stationary phase design.[84–89]

5. Novel materials

Rappe has invoked the participation of π-stacking interactions to explain the behavior of polymerization catalyst **159**. This catalyst is unusual in that it produces blocks of isotactic and atactic products during the polymerization of polypropylene. A conformational study using the UFF force field suggested the existence of π-stacking interactions present in one of the rotameric forms of the catalyst contributes to this outcome.[90] As part of a program directed towards novel liquid crystalline materials, Grubbs has recently investigated the effect of electrostatic interactions between polymer bound triphenylene **160** and perfluoroarene **161**. Clear evidence of electrostatic interaction was obtained from DSC studies, which in turn drive **160** to crystalization.[91]







6. Conclusions

The concepts of π shielding and π stacking continue to be invoked to explain the outcome of numerous regiochemical and stereochemical processes. As we begin to understand the origins of these interactions, it will become possible to design processes which harness their full potential, both in organic synthesis and materials chemistry. As can be seen from this survey, there is much to be gained from proper insight and the application of these design principles, and numerous discoveries await.

As a case in point, a very recent report from the MacMillan laboratories describes the catalytic activity of benzyl imidazolidinone **162** (Scheme 50). Among numerous reactions this 'metal-free' species catalyzes, the asymmetric Friedel–Crafts is particularly noteworthy, giving substituted pyrrole **163** in 97% ee. A working hypothesis, supported by MM3 modeling, suggests that π-shielding of the cinnamaldehyde derived imiminium ion (by the benzyl group) contributes to facial selectivity, as shown in **164**.[92]

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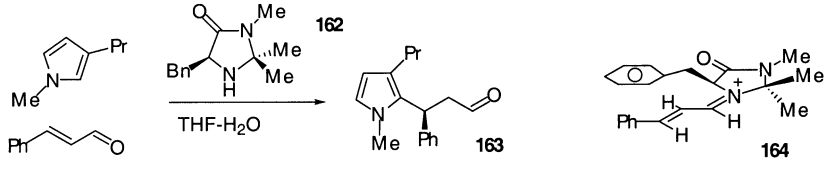

Scheme 50.

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Biographical sketch

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