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Diels–Alder reactions on solid supports

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1. Introduction

The Diels–Alder reaction is a concerted [$4\pi+2\pi$] cycloaddition reaction of a conjugated diene and a dienophile. This reaction belongs to the larger class of pericyclic reactions, and provides several pathways towards the simultaneous construction of substituted cyclohexenes with a high degree of regioselectivity, diastereoselectivity and enantioselectivity. Surveys on Diels–Alder reactions can be found in several excellent review articles.[1–4] Since its discovery in 1928, the Diels–Alder reaction has been amongst the most important carbon–carbon bond forming reactions available.[5] The development of solid-phase organic chemistry has progressed rapidly during recent years, and copious solid-phase synthesis methods have been utilised in combinatorial chemistry.[6,7] Therefore, it is not surprising that several examples of solid-supported Diels–Alder reactions have been reported recently in the literature. This review includes examples of many types of Diels–Alder reactions, including classical intermolecular, inverse electron demand, hetero and intramolecular Diels–Alder reactions that have been performed on solid—mostly polymeric—support. This review covers the literature until June 2000.

2. Intermolecular Diels–Alder reactions with polymer-supported dienes

2.1. Normal Diels–Alder reactions

One of the first examples of utilising cyclopentadienylated polystyrene as a diene component in the Diels–Alder reaction was reported by Miura and co-workers.[8] The cyclopentadienylated polystyrene **1** was prepared by reacting styrene–chloromethylstyrene co-polymer **2** with cyclopentadiene **3** in the presence of sodium in THF (Scheme 1). This procedure gives polymer-supported sodium cyclopentadienide that is inactive for the Diels–Alder cycloaddition reaction. Treatment of polymer-supported

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Abbreviations: Ac, acetyl; BINOL, binaphthol; Bn, benzyl; BOC, butyloxycarbonyl; Bz, benzoyl; CBZ, benzyloxycarbonyl; DCB, 1,3-dichlorobenzene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; de, diastereomeric excess; DEB, diethylbenzene (a mixture of 1,2, 1,3 and 1,4 isomers); DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; ee, enantiomeric excess; fod, 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadienoate; FMOC, 9-fluorenylmethyloxycarbonyl; KHMDS, potassium salt of hexamethyldisilazane; LAH, lithium aluminium hydride; nOe, nuclear Overhauser enhancement; PFPTFA, pentafluorophenyl trifluoroacetate; Pn, pentyl; PNA, phenyl β-naphthylamine; PTFE, poly(tetrafluoroethylene); py, pyridine; Pyr, pyridyl; TBAF, *n*-tetrabutylammonium fluoride; TEA, triethylamine; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMS, trimethylsilyl; Trt, trityl; Ts, tosyl.

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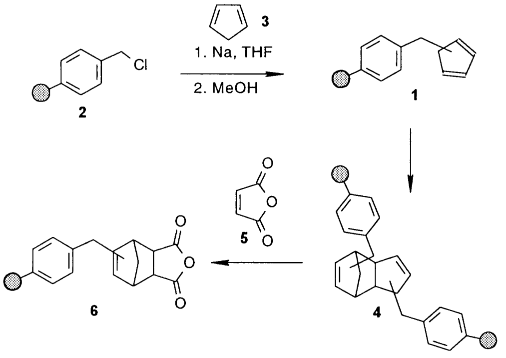
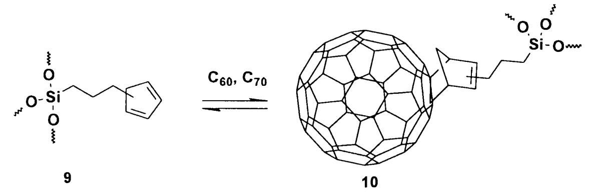


Scheme 1.

cyclopentadienide with methanol converts it to the corresponding polymer-bound cyclopentadiene **1** that is capable of undergoing the cycloaddition reaction at 80°C to give the cross-linked resin **4**. The cross-linked cyclopentadienylated polymer **4** was then heated with maleic anhydride **5** in nitrobenzene at 180°C to give the soluble polymer **6** with repeated bicyclo[2.2.1]-5-hepten-2,3-dicarboxylic anhydride moieties resulting from the consecutive retro-Diels–Alder and Diels–Alder reactions of **4**. The product **6** turned out to be a thermoreversible, cross-linked polymer as determined by the DSC curves. Interestingly, when the cyclopentadienylation of **2** was attempted by allowing it to react with preprepared sodium cyclopentadienylide at 10°C, an extensive gelation occurred due to cross-linking by the intermolecular Diels–Alder reaction between cyclopentadienylated polystyrene units.

In a study by Rotello et al.[9] buckminsterfullerene C_{60} was covalently attached to the cyclopentadiene-functionalised Merrifield resin **7** (Scheme 2). In this example, cyclopentadienylated resin was prepared successfully by allowing the Merrifield resin **7** to react with an excess of sodium cyclopentadienylide in toluene at −20°C. The functionalised polystyrene reacted with C_{60}, even at room temperature, to yield the buckminsterfullerene polymer **8**. On heating at 180°C in decalin, resin **8** released C_{60}. According to the authors, the cycloaddition/cycloreversion process is truly reversible. The Diels–Alder and retro-Diels–Alder sequence can be repeated. Finally, the authors provided further evidence for the Diels–Alder cycloaddition reaction of **7** by reacting it with such reactive dienophiles as maleic anhydride and tetracyanoethylene.

Nie and Rotello[10] have found a very elegant application for the solid-supported fullerene cycloadducts. Fullerenes can be purified non-chromatographically by the thermoreversible Diels–Alder cycloaddition reaction. Chloropropyl-functionalised silica gel was reacted with lithium cyclopentadienylide to give the solid-supported diene **9** (Scheme 3), which underwent the cycloaddition reaction with C_{60}/C_{70} soot mixtures to afford the mixed fullerene cycloadducts **10**. Heating of this mixture in toluene released the immobilised fullerenes C_{60} (96% pure) and C_{70} free from non-fulleroid, polycyclic aromatic hydrocarbons. Since there is an approximate 3.5-fold difference in the Diels–Alder reactivity between C_{60} and C_{70}, this method is likely to provide a useful means of enriching and separating individual fullerene species.

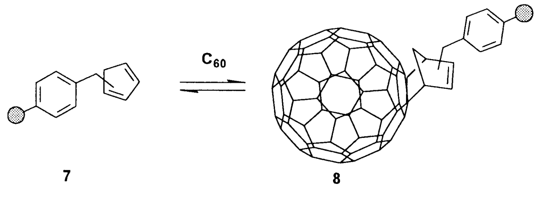


Scheme 3.

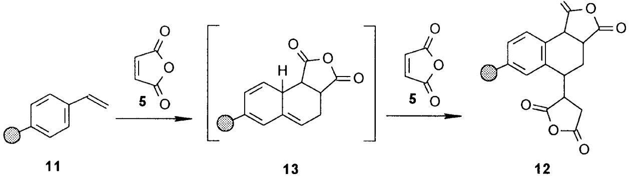
Stranix and Darling[11] used vinylpolystyrene **11** as a diene component in its Diels–Alder reactions with various olefins, including maleic anhydride, *N*-ethylmaleimide and fumaryl chloride. The cycloaddition reaction between vinylpolystyrene **11** and maleic anhydride **5** gave the biscycloadduct **12** via an initial [4π+2π] cycloaddition reaction and subsequent ene reaction (Scheme 4). The intermediate resin-bound cycloadduct **13** rearomatises, providing the driving force for the ene reaction that finally produces the bisadduct **12**. The authors additionally prepared magnetically-recoverable beads from the macroporous resin by loading it with magnetic iron oxide before or after the cycloaddition reaction of the dienoic resin with an appropriate dienophile.

In work reported by Rotello et al.[12] buckminsterfullerene C_{60} was attached to the furan-functionalised resin. Merrifield resin was initially reacted with the sodium alkoxide of furfuryl alcohol in toluene to give the diene resin **14**. This resin **14** reacts with C_{60}, even at room temperature, to afford the fullerene-functionalised polystyrene **15** (Scheme 5). The reaction is reversible, providing 80% recovery of C_{60} upon heating **15** at 180°C with an excess of maleic anhydride. This reversible, covalent attachment of buckminsterfullerene to the resin-bound furfuryl alcohol **14** is more efficient than the attachment of C_{60} to the previously studied cyclopentadiene resin **7**.[9] Additionally, this represents an improved method for non-chromatographic purification of fullerene mixtures.

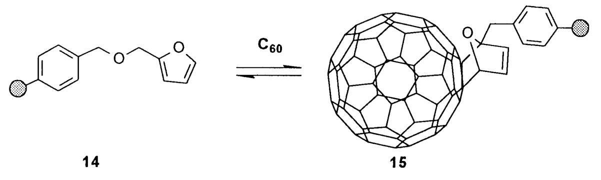
Schlessinger and Bergstrom[13] have reported several diastereoselective Diels–Alder reactions of resin-bound nonracemic siloxyaminofuran dienes with methyl acrylate. The co-polymer of 1% divinylbenzene with styrene was



Scheme 2.



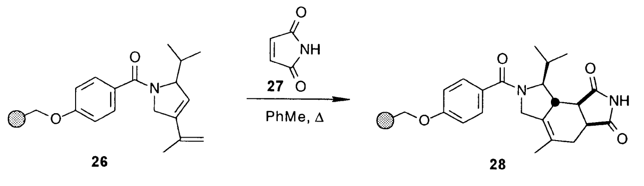
Scheme 4.



Scheme 5.

elaborated to the corresponding chlorodi-*i*-propylphenylsilane polystyrene via a lithiation/silylation sequence. The chlorosilane resin **16** was treated with the potassium enolate of non-racemic 3-amino-2(5*H*)-furanone **17** to provide the resin-bound 3-aminofuran **18** in high yield (Scheme 6). It was subsequently reacted with methyl acrylate **19** to give the cycloadduct **20**. The resin-bound *endo* cycloadduct **20** was then subjected to TBAF treatment to give the substituted amino cyclohexenone **21** in 94% yield (two steps). To determine the diastereoselectivity of the Diels–Alder reaction, **20** was further converted to **22**. The subsequent chiral HPLC analysis of **22** proved its enantiomeric purity to be >99%. The *endo* adduct was thus formed in the cycloaddition reaction in >99% diastereomeric excess.

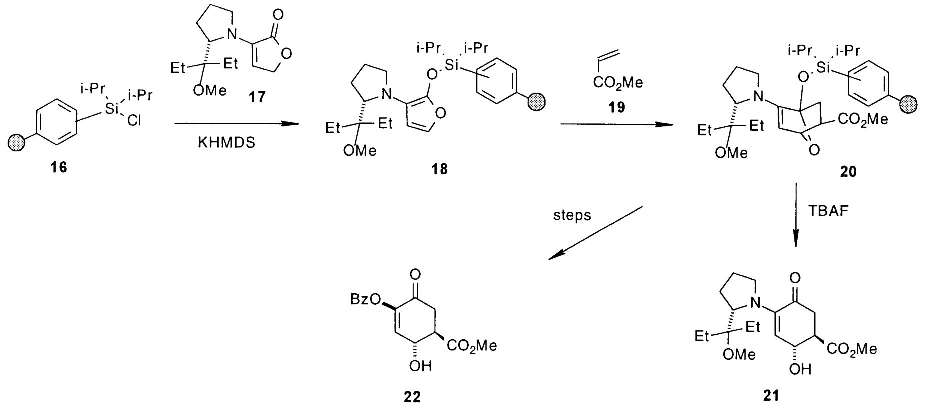
A similar type of Diels–Alder reaction between the resin-bound 3-bromo-2-aminofuran **23** and methyl acrylate **19** is presented in Scheme 7. Subsequent TBAF treatment of the immobilised **24** gave the substituted 3-bromo-4-amino-2(5*H*)-furanone **25** in 93% yield (two steps), the diastereomeric excess of the *endo* cycloadduct **24** again being >99%.[13] The authors further investigated the Diels–Alder reactions of **18** and **23** with other dienophiles, such as dimethyl fumarate, dimethyl maleate, acrylonitrile, and phenyl vinyl sulphone.



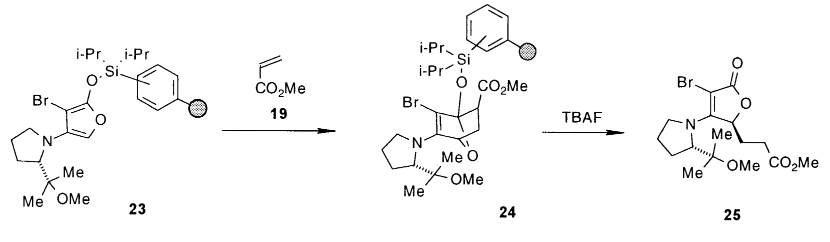
Scheme 8.

In a paper by Heerding et al.[14] an effective intramolecular ruthenium-catalysed ene–yne metathesis reaction was used in tandem with the intermolecular Diels–Alder reaction. An example of this reaction sequence is presented in Scheme 8. The chloro-Wang resin-bound pyrroline diene **26** was allowed to react with maleimide **27** in toluene at 105°C to afford the resin-bound hexahydroisoindole derivative **28** as a single isomer. The ^{1}H NMR spectra and nOe studies of hexahydroisoindole cleaved from resin **28** indicate that the resin does not affect the stereochemistry of the cycloaddition reaction. By using the split and mix methodology and the ene–yne metathesis/Diels–Alder sequence, the authors prepared a combinatorial library, which contained, theoretically, 4,200 functionalised isoindoles.

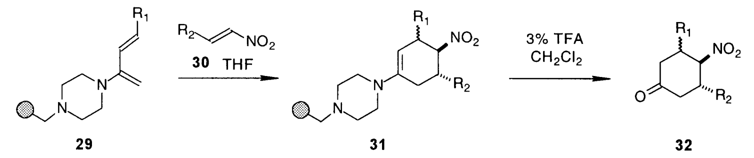
A useful method for preparing 3,4,5-trisubstituted cyclohexanones has been presented by Hird et al.[15] The resin-bound 2-piperazinylbutadienes[16] **29** underwent a Diels–Alder reaction with *trans*-2-nitrostyrenes **30** to afford a mixture of diastereomeric cycloadducts **31** (Scheme 9, Table 1). These were hydrolysed with 3% TFA in CH_2Cl_2 to give the substituted 4-nitrocyclohexanones **32** in good yield and purity. In the same study, the 2-aminobutadiene resins **29** were additionally allowed to react with substituted maleimides **33** to give both *endo* and *exo* cycloadducts **34** as



Scheme 6.



Scheme 7.



Scheme 9.

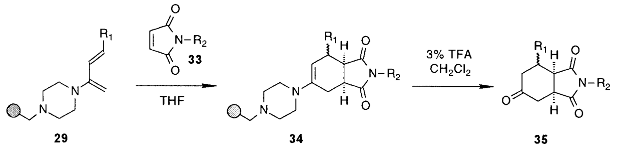
Table 1. Cycloaddition reaction of 2-aminobutadiene **29** with *trans*-2-nitrostyrene **30**

Compound	R_1	R_2	Yield[a] (%)	Purity[b] (%)
32a	4-MeOPh	Ph	45	94
32b	4-MeOPh	4-NO_2Ph	54	87
32c	4-BrPh	Ph	63	90
32d	4-FPh	4-BrPh	58	91
32e[c]	3-Pyr	4-MeOPh	52	98
32f[c]	4-BrPh	3-CF_3Ph	31	91
32g[c]	4-BrPh	Ph	33	88

[a] Yields are based on the loading of the Merrifield resin used.
[b] HPLC.
[c] Automated synthesis.

approximately equimolar mixtures (Scheme 10, Table 2). This is in contrast to the corresponding solution-phase reaction of *N*-phenylmaleimide that is reported to afford exclusively the *endo* cycloadduct.[17] The reason for this anomalous reactivity is probably the non-concerted reaction pathway due to the enamine character of the 2-aminobutadienes used. Whether the attachment of the aminodiene to the resin affects the cycloaddition mechanism, is currently not known. Finally, acid-catalysed cleavage from the resin gave the octahydroisoindole derivatives **35** in good yield.

Barrett et al.[18] obtained dienyl ethers **37** by Tebbe olefination of the resin-bound α,β-unsaturated acrylate esters **36**.[19,20] The polymer-bound dienyl ethers **37** were allowed to react with *N*-methylmaleimide **38**, dimethyl fumarate **39**, 2-chloroacrylonitrile **40**, 2-ethylacrolein **41**, methyl vinyl ketone **42** and methyl 2-butenyl ketone **43** to produce immobilised cyclohexenes **44** (Scheme 11, Table 3). The resin-bound cycloadducts **44** were treated with 1% TFA in CH_2Cl_2 to give the corresponding cyclohexanones **45**. The authors reported high *endo* selectivity for the cycloaddition reaction between **37** and *N*-methylmaleimide **38**. This observation is consistent with the solution-phase Diels–Alder reactions of 2-silyloxydienes with maleimides[21] and in contrast to the cycloaddition reactions of 2-piperazinylbutadienes attached to the resin.[15]



Scheme 10.

Table 2. Cycloaddition reaction of 2-aminobutadiene **29** with substituted maleimide **33**

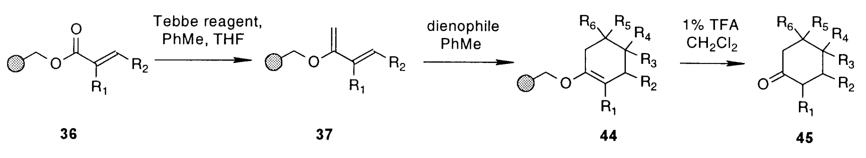
Compound	R_1	R_2	Yield[a] (%)	Purity[b] (%)
35a	Ph	Me	87	69
35b	Ph	4-BrPh	81	93
35c	Ph	4-AcPh	75	88
35d	4-FPh	4-BrPh	58	91
35e	4-MeOPh	Ph	53	90
35f[c]	*t*-Bu	4-(MeO_2CPh)CH_2	38	95
35g[c]	4-FPh	4-BrPh	37	86
35h[c]	4-MeOPh	4-EtPh	43	88

[a] Yields are based on the loading of the Merrifield resin used.
[b] HPLC.
[c] Automated synthesis.

Smith[22] prepared several immobilised Danishefsky silyloxydienes by reacting enolisable α,β-unsaturated aldehydes and ketones with the activated polystyrene diethylsilane triflate resin **46** in CH_2Cl_2 in the presence of Hünig's base. The α,β-unsaturated ketone **47** was converted to the resin-bound 2-silyloxy-1,3-butadiene **48**, which was allowed to react with *N*-phenylmaleimide **49**. The resultant cycloadduct was cleaved from the diethylsilyl resin with TFA to give 98% pure cyclohexanone **50** in 63% yield (Scheme 12). In the same study, the α,β-unsaturated aldehyde **51** was converted to 1-silyloxy-1,3-butadiene **52** (Scheme 13). The immobilised silyloxydiene **52** was then subjected to a Diels–Alder reaction with *N*-phenylmaleimide **49** to produce the resin-bound cycloadduct. The substituted cyclohexenol **53** was isolated as the final product in 83% yield (HPLC purity 95%) after the TFA cleavage. Several additional examples of the solid-phase cycloaddition reactions of silyloxydienes were described in the original article.[22]

Wendeborn et al.[23] developed a very efficient cascade of reactions for the preparation of small molecule libraries of complex, chiral and highly functionalised compounds. The sequence of these reactions includes the epoxidation of polystyrene-supported 3,5-cyclohexadiene-1,2-diol, a nucleophilic ring-opening reaction, Stille/Suzuki cross-coupling reactions and a Diels–Alder reaction. The polymer-bound dienes **54** and **57** obtained from the Stille coupling were reacted with *N*-(3-iodophenyl)maleimide **55** and naphthoquinone **58** to give the cycloadducts **56** and **59** with complete facial and *endo* selectivity in 72 (purity 95%) and 96% (purity >90%) yields, respectively (Schemes 14 and 15). The *endo* selectivity can be explained by the effect of the bulky ketal group blocking the β-face of the polymer-supported diene.

Craig et al.[24] reported the use of a hydroxymethylpolystyrene-supported *o*-quinodimethane precursor **60** in the [4π+2π] cycloaddition reaction with benzoquinone **61** and dimethyl acetylenedicarboxylate **62** (Scheme 16). These reactions gave 2,3-naphthoquinone **63** and dimethyl naphthalene-2,3-dicarboxylate **64** in 39 and 41% yields, respectively. The authors suggest that 2,3-naphthoquinone **63** is derived from the sequence of the [4π+2π] cycloaddition,

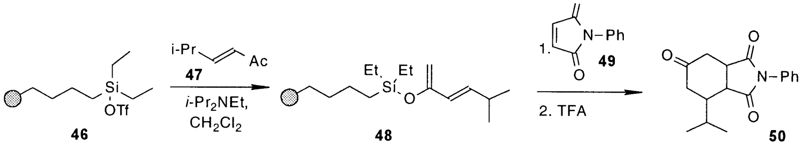


Scheme 11.

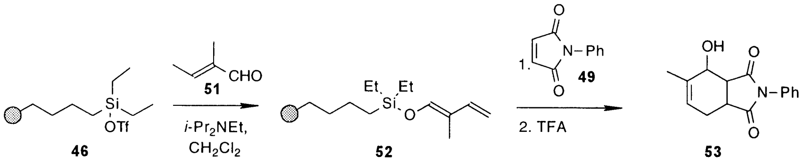
Table 3. Cycloaddition reaction of dienyl ethers **37** with maleimides and other dienophiles

Compound	R_1	R_2	Dienophile	Diastereoselectivity	Yield[a] (%)
45a	H	Ph	*N*-Me-maleimide **38**	97:3	30
45b	H	Me	*N*-Me-maleimide **38**	97:3	30
45c	H	Et	*N*-Me-maleimide **38**	97:3	18
45d	H	Pr	*N*-Me-maleimide **38**	97:3	27
45e	H	$Me(CH_2)_6$	*N*-Me-maleimide **38**	7:3	35
45f		$-(CH_2)_4-$	*N*-Me-maleimide **38**	97:3	51
45g	H	Ph	*E*-$MeO_2CCH{=}CHCO_2Me$ **39**	1:1	17
45h	H	Ph	$H_2C{=}CClCN$ **40**	7:3	23
45i	H	Ph	$H_2C{=}CEtCHO$ **41**	5:3	21
45j	H	Ph	$H_2C{=}CHAc$ **42**	7:3	44
45k	H	Me	$H_2C{=}CHAc$ **42**	5:3	11
45l	H	$Me(CH_2)_6$	$H_2C{=}CEtCHO$ **41**	3:1	19
45m	H	$Me(CH_2)_6$	$H_2C{=}CEtAc$ **43**	4:1	22
45n		$-(CH_2)_4-$	$H_2C{=}CEtCHO$ **41**	2:2:1:1	20
45o		$-(CH_2)_4-$	$H_2C{=}CHAc$ **42**	3:2	43

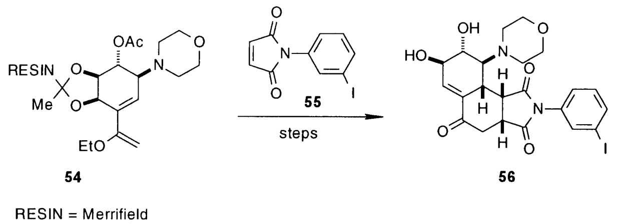
[a] Cleavage with 1% TFA in $CDCl_3$ and $(Me_3Si)_2O$ as a reference.



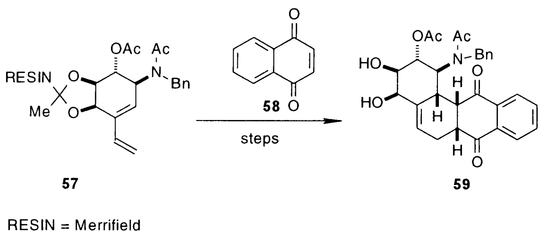
Scheme 12.



Scheme 13.



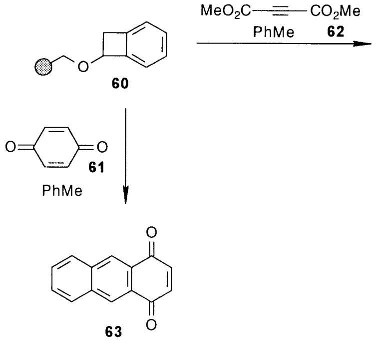
Scheme 14.



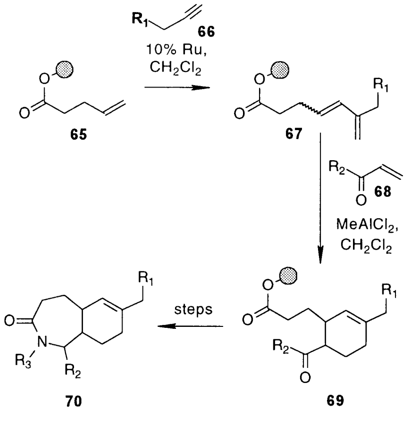
Scheme 15.

elimination, and oxidation reactions. The cycloadducts were released directly into the solution when the *o*-quinodimethane was thermally formed from the precursor resin **60**. The driving force for the Diels–Alder reaction was provided by the aromatisation of the cycloadduct intermediate.

Schürer and Blechert[25] developed an efficient ruthenium-catalysed yne–ene cross-metathesis and Diels–Alder cycloaddition sequence to prepare various substituted cyclohexenes and octahydrobenzo[*c*]azepin-3-ones. The ruthenium-catalysed cross-metathesis reaction of the Merrifield resin-bound 4-pentenoate **65** with a terminal alkyne **66** gave the 1,3-diene **67** that was used in the subsequent Diels–Alder reaction with the alkyl vinyl ketone **68** or acrolein in the presence of $MeAlCl_2$ in CH_2Cl_2/PhMe (Scheme 17, Table 4). The resulting cycloadducts **69** were further elaborated to the desired octahydrobenzo[*c*]-azepin-3-ones **70**.



Scheme 16.

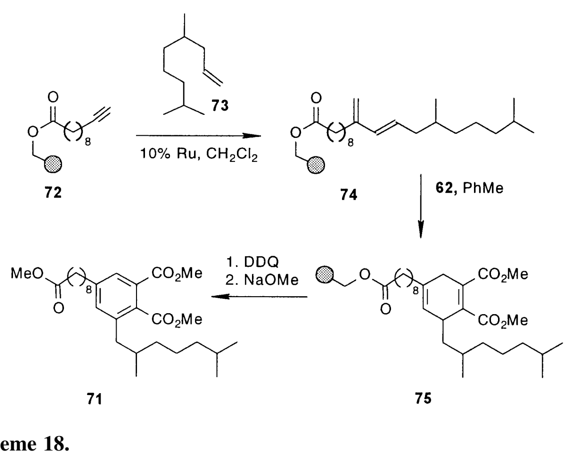


Scheme 17.

Table 4. Preparation of 1,2,7-trisubstituted octahydrobenzazepinones

Compound	R_1	R_2	R_3	Yield[a] (%)
70a	$CH_3(CH_2)_4$	Me	Bn	19
70b	$CH_3(CH_2)_4$	Me	$PhCH_2CH_2$	28
70c	$CH_3(CH_2)_4$	Me	Me	20
70d	$CH_3(CH_2)_4$	H	Bn	22
70e[b]	$HOCH_2$	H	$PhCH_2CH_2$	15
70f[b]	$HOCH_2$	H	Bu	15
70g[b]	$HOCH_2$	H	Me	15
70h	BnO	H	Me	14
70i	Me(CBZ)N	H	Me	15

[a] Mass balance yield of purified material.
[b] The hydroxy group is Trt-protected in the cycloaddition step, and is deprotected before cleavage of the product from the resin.



Scheme 18.

The same authors[25] prepared the polymer-bound dimethyl phthalate **71** (Scheme 18). The yne–ene cross-metathesis reaction of the resin-bound **72** with olefin **73** gave the polymer-bound diene **74**. The subsequent Diels–Alder reaction with dimethyl acetylenedicarboxylate **62** as a dienophile afforded tetrasubstituted 1,4-cyclohexadiene **75**. Oxidation of **75** with DDQ, and nucleophilic cleavage afforded **71** in 36% yield.

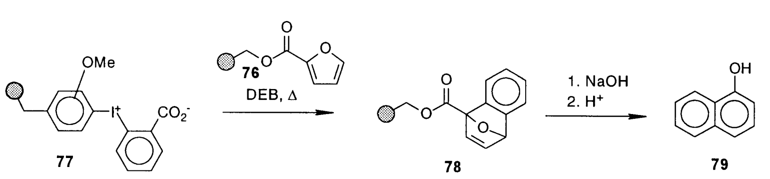
Finally, Gaviña et al.[26] introduced a very interesting Diels–Alder reaction between the Merrifield resin-bound furoate diene **76** and the benzynic dienophile generated in situ by thermal decomposition of the resin-bound diphenyliodonium-2-carboxylate **77** in diethylbenzene (Scheme 19). The polymer-bound bridged cycloadduct **78** was converted to 1-naphthol **79** in 62% yield after saponification and subsequent acidification.

2.2. Hetero Diels–Alder reactions

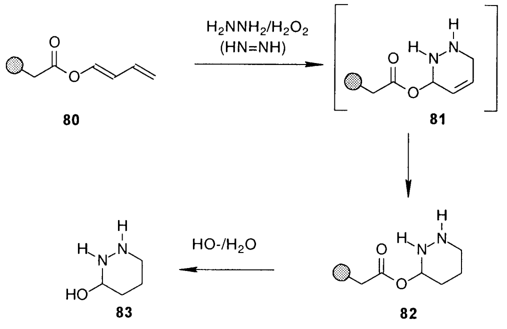
Gaviña et al.[27] reacted the polymer-bound diene **80** with diimine that was generated in situ from hydrazine hydrochloride in the presence of hydrogen peroxide. The Diels–Alder reaction gave the immobilised cycloadduct **81** that was instantaneously reduced to **82** (Scheme 20). The cycloadduct **83** was isolated after hydrolysis in 18% yield. A related three-phase cycloaddition reaction between the polymer-bound diene **80** and diimine generated from its polymer-supported precursor **84** gave the desired resin-bound cycloadduct **81** (Scheme 21).

Brown et al.[28] attached benzylidenepyruvic acid to the Wang resin to give the immobilised 1-oxabutadiene **85** that was subsequently allowed to react with a number of substituted vinyl ethers **86** as electron-rich dienophiles (Scheme 22). This inverse electron demand hetero Diels–Alder reaction was catalysed by $Eu(fod)_3$ and gave the resin-bound pyranyl cycloadducts **87**. These were reductively cleaved from the resin by LAH to give *endo*-**88** and *exo*-**88** diastereomers in moderate to excellent yields (Table 5). The authors report that the *endo*/*exo* selectivity is approximately the same both under solid-phase and under homogeneous solution-phase reactions, the favoured diastereomer being the *endo* adduct. Moreover, the yields of the pyranyl cycloadducts seem to be higher under solid-phase than under liquid-phase conditions. The Diels–Alder reactions between the resin-bound diene **85** and the slightly less reactive dienophiles of styrene structure, however, gave significantly lower yields than the corresponding solution-phase reactions. The authors suggest that there may be unfavourable interactions in the *endo* transition-state structures between the polymeric support and the aromatic nuclei of the styrene dienophiles.

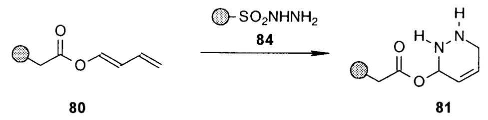
A 100-member β-strand mimetics library of aza Diels–Alder adducts **89** was constructed by employing the cycloaddition reaction between a resin-bound substituted pentadienoic acid amide **90** and the 3,5-pyrazolinedione generated in situ from the 3,5-pyrazolidinedione **91**.[29] [Bis(trifluoroacetoxy)iodo]benzene was used for the in situ oxidation reaction (Scheme 23). In this example, the cycloaddition reactions gave *cis* isomers but were non-stereoselective. The authors also presented an improved



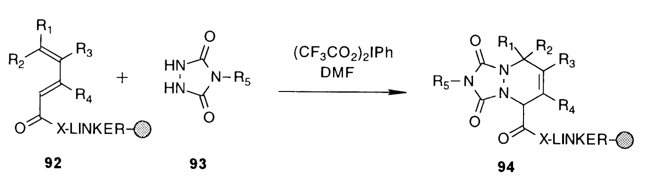
Scheme 19.



Scheme 20.



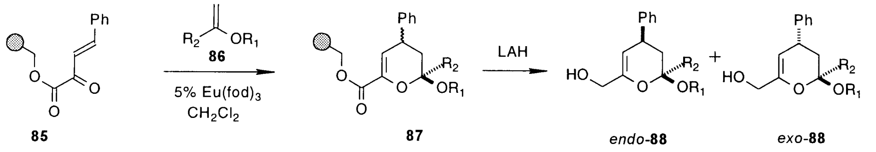
Scheme 21.



Scheme 24.

version of the cycloaddition reaction, in which they allowed the immobilised pentadienoic acids **92** to react with 1,2,4-triazolinediones generated in situ from the urazole **93** (Scheme 24). Kahn et al.[29] report that these *cis*-selective Diels–Alder reactions gave consistently >90% pure cycloadducts **94** in high yields. Boldi et al.[30] used a very similar approach in the synthesis of triazolopyridazines by allowing Rink amide polystyrene-bound pentadienoic acids to react with *N*-substituted urazines.

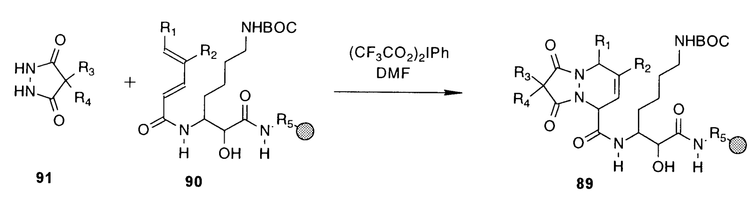
Panek and Zhu[31,32] reported inverse electron demand Diels–Alder reactions of resin-bound 3,6-disubstituted 1,2,4,5-tetrazines with electron-rich dienophiles. Polystyrene–COCl resin **95** was initially esterified with the tetrazine **96**, and subsequently elaborated to methyl sulfide azadiene **97** and methyl sulfone azadiene **98** (Scheme 25). The azadiene **97** was allowed to react with electron-rich enamines **99**, dihydrofuran **99g**, and dihydropyran **99h** while resin-bound azadiene **98** was reacted with terminal alkynes **102** and silyl enol ethers in 1,4-dioxane (Schemes 26 and 27, Tables 6 and 7). The authors were able to prepare both regioisomers of 1,2-diazine by using resin-bound tetrazines **97** and **98**, the methylsulfonyl group of **98** being more electron withdrawing than the thiomethyl moiety of **97**. The regiochemical course of the inverse electron demand Diels–Alder reaction reverses when the thiomethyl moiety of **97** is converted to the methylsulfonyl group of **98**. The cycloadducts **101** and **104** were cleaved from the resins **100** and **103**, respectively, by basic hydrolysis.



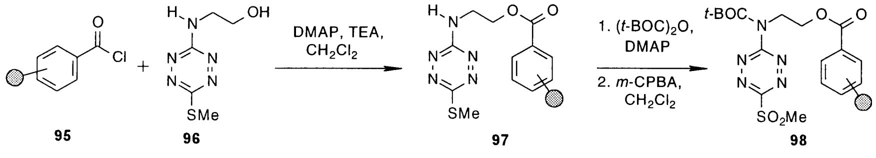
Scheme 22.

Table 5. Preparation of substituted dihydropyrans by hetero Diels–Alder reactions

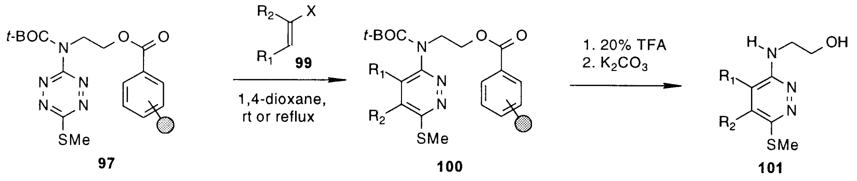
Compound	R_1	R_2	*endo*:*exo*	Yield (%)
88a	Et	H	>97:3	100
88b	*i*-Bu	H	96:4	92
88c	cyclohexyl	H	>97:3	100
88d	*t*-Bu	H	74:26	92
88e	$(CH_2)_4OH$	H	94:6	82
88f	Me	Me	80:20	100
88g	Me	β-naphthyl	74:26	62
88h	Et	EtO	-	86



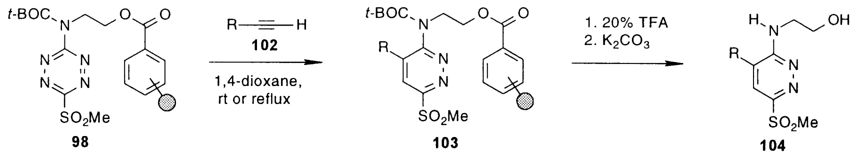
Scheme 23.



Scheme 25.



Scheme 26.



Scheme 27.

Table 6. Cycloaddition reactions of resin-bound azadiene **97**

Dienophile	R_1	R_2	X	Ratio[a]	Yield of **101**[b] (%)
99a		$-(CH_2)_3-$	1-Pyrrolidinyl		82
99b		$-(CH_2)_5-$	1-Pyrrolidinyl		79
99c	H	H	2-oxo-1-Pyrrolidinyl		61
99d	H	Me	1-Pyrrolidinyl	4:1	67
99e	H	Ph	1-Pyrrolidinyl		35
99f	H	4-MeO–Ph	1-Pyrrolidinyl		30
99g		$-CH_2CH_2O-$	–	1:2	47
99h		$-(CH_2)_3O-$	–	2:1	28

[a] The regioisomer ratio was determined by ^{1}H NMR of the crude products.

[b] The yields are based on the loading level of polystyrene–CO_2H.

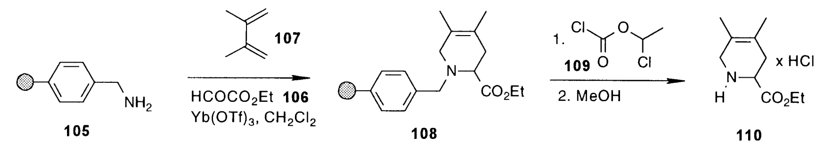
A very effective $Yb(OTf)_3$-catalysed solid-phase aza Diels–Alder reaction was found to take place when aminomethylated polystyrene resin **105**, aldehyde **106**, diene **107**, and $Yb(OTf)_3$ were allowed to react in CH_2Cl_2 (Scheme 28).[33] The in situ-generated imines reacted with various dienes, such as 2,3-dimethyl-1,3-butadiene **107**, isoprene, butadiene and 2-methyl-1,3-pentadiene. The aldehyde components used were ethyl glyoxylate **106**, formaldehyde and phenylglyoxal hydrate. The aza cycloadducts **110** were cleaved from the resin **108** using traceless cleavage that utilised *N*-dealkylation by 1-chloroethyl chloroformate **109** and subsequent methanolysis of the resulting carbamate to give the debenzylated piperidine derivatives **110** with intact double bonds.

Table 7. Cycloaddition reactions of resin-bound azadiene **98**

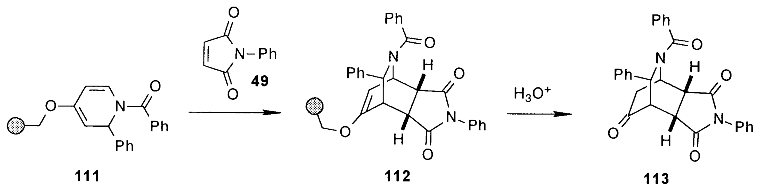
Dienophile	R	Yield of **104**[a] (%)
102a	CH_2OBn	50
102b	OEt	72
102c	CH_2NBnMe	31
102d	CH=CHOMe	66
102e	Ph	72

[a] The yields are based on the initial loading level of polystyrene–CO_2H.

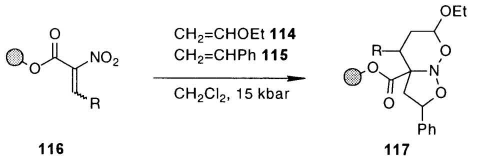
Chen and Munoz[34] have reported the use of various resin-bound *N*-acyl enol ether dienes[35] **111** in stereospecific Diels–Alder reactions with dienophiles such as maleimides, diethyl azodicarboxylate, and β-nitrostyrene, affording 2-acyl-3,7,8-substituted-5-oxo-2-azabicyclo[2.2.2]-octanes



Scheme 28.



Scheme 29.



Scheme 30.

and the triaza analogues. When *N*-phenyl maleimide **49** was used as a dienophile, only the resin-bound *endo* diastereomer **112** was formed (Scheme 29). The resin **112** was first treated with aqueous 1 M TFA solution to remove the unreacted diene and then with 12 M solution of HCl in tetrahydrofuran to afford **113** in 32% yield.

An interesting three-component tandem [4π+2π]/[3π+2π] cycloaddition reaction has been described by Kuster and Scheeren.[36] The high pressure-promoted cycloaddition reaction of ethyl vinyl ether **114** as dienophile, styrene **115** as dipolarophile and the resin-bound nitroalkene **116** (R=Ph, 3-Pyr, 1-furyl, 1-pyrrolyl, *i*-Pr) as heterodiene gave the resin-bound adducts **117** (Scheme 30). LAH reduction of **117** gave the corresponding hydroxymethyl-substituted nitrosoacetals in moderate yields.

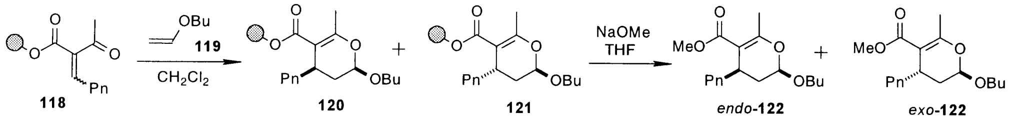
Tietze et al.[37] used the inverse electron demand hetero Diels–Alder reaction between polymer-supported (Merrifield) oxabutadienes and vinyl enol ethers to prepare methyl 3,4-dihydro-2*H*-pyrancarboxylates. The reaction between the polystyrene-bound hetero diene **118** and butyl vinyl ether **119** in CH_2Cl_2 at 60°C for 3 days, for example, gave the diastereomeric cycloadducts **120** and **121**. These were treated with NaOMe to give *endo*-**122** and *exo*-**122** in 32% yield (Scheme 31), the *endo*/*exo* ratio being 5:1.

Craig et al.[24] generated polymer-bound *o*-quinodimethane from the precursor resin **60** and allowed it to react with various dienophiles, such as 4-nitrobenzaldehyde, 4-bromobenzaldehyde, methyl glyoxylate, and *N*-tosyl imines. Both Brønsted and Lewis acid treatment of the cycloadduct resin afforded dihydrobenzopyrans and substituted tetrahydroisoquinolines. An example of this Diels–Alder reaction is the cycloaddition between *o*-quinodimethane generated from **60** and *N*-tosylbenzaldimine **123** to give the resin-bound intermediate **124** at 105–110°C (Scheme 32). The cycloadduct was released from resin **124** by $SnCl_4$ and allyltrimethylsilane to afford the allyltetrahydroisoquinoline **125** in 47% yield.

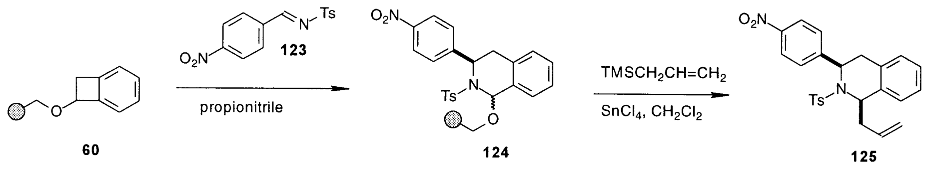
3. Intermolecular Diels–Alder reactions with polymer-supported dienophiles

3.1. Normal Diels–Alder reactions

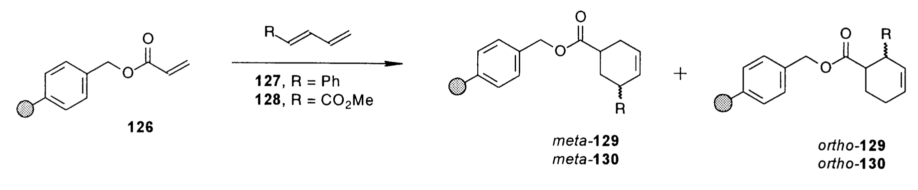
There are several reports on the use of polystyrene or resin-bound acrylates as dienophiles in the Diels–Alder reactions. In one of the first examples, Yedidia and Leznoff[38] prepared the benzyl acrylate resin **126** by treating a 1% cross-linked divinylbenzene-styrene co-polymer that contained benzyl



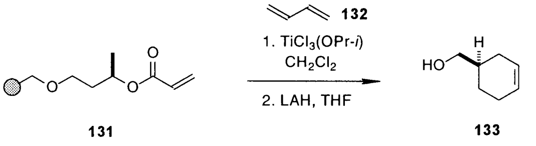
Scheme 31.



Scheme 32.



Scheme 33.



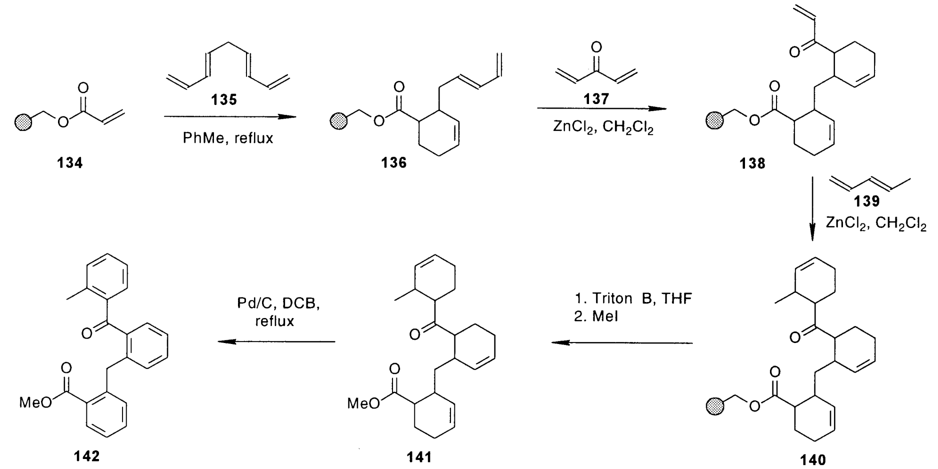
Scheme 34.

alcohol groups with acryloyl chloride. The acrylate resin **126** was subjected to the Diels–Alder reaction with *E*-1-phenyl-1,3-butadiene **127** and methyl *E*-2,4-pentadienoate **128** to give the cycloadducts **129** and **130** in 80 and 52% yields, respectively (Scheme 33). The *ortho*/*meta* regioselectivities were similar to the corresponding solution-phase reactions, the *ortho* isomers being favoured. The cycloadduct **129** was produced as a 94:6 mixture of *ortho* and *meta* isomers, and cycloadduct **130** as a 77:23 isomeric mixture.

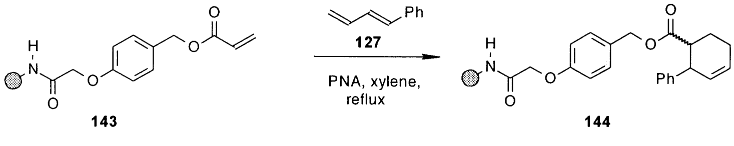
Leznoff et al.[39] employed the Merrifield resin-bound chiral acrylate **131** in the asymmetric Diels–Alder reaction with 1,3-butadiene **132**, using titanium trichloride isopropoxide as a Lewis acid catalyst (Scheme 34). The (*R*)-cycloadduct **133** was obtained after LAH reduction in a modest ee of 23.4%, comparable to the ee of 20.5% obtained from the corresponding solution-phase reaction.

Winkler and Kwak[40] used (hydroxymethyl)polystyrene resin to prepare the polymer-bound acrylate **134**. This acrylate was subsequently used in an iterative Diels–Alder cycloaddition with the bisdiene **135** in refluxing toluene to afford the dienoic cycloadduct **136** as a 1:2 mixture of *cis* and *trans* isomers (Scheme 35). The diene **136** was then allowed to react with bisdienophile, divinylketone **137**, in the presence of $ZnCl_2$ to give **138**, which in another Diels–Alder reaction with 1,3-pentadiene **139**, afforded the cycloadduct **140**. Interestingly, the authors report that the overall yield of the triple Diels–Alder sequence is >65%, compared to a 24% overall yield in solution. The cycloadduct **141** was obtained after treatment of the resin-bound product **140** with Triton B and iodomethane. Finally, on treating **141** with Pd/C in *m*-dichlorobenzene, only a single aromatic product **142** was obtained, proving that only one regioisomer was formed in a cascade of the Diels–Alder reactions.

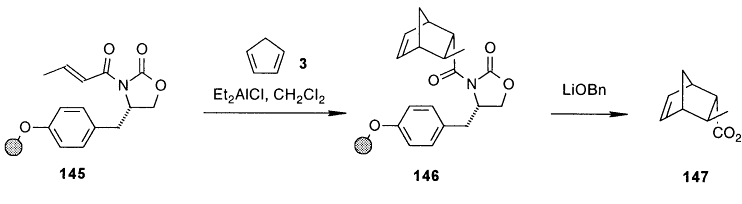
Zhao et al.[41] grafted polystyrene radiolytically onto inert fluoropolymer microtubes to be used in solid-supported organic reactions at high temperatures. The 4-(hydroxymethyl)phenoxyacetic acid-functionalised amino(polytetrafluoroethylene) tubes reacted with acryloyl chloride in the presence of TEA in CH_2Cl_2 to give the tube-bound dienophile **143**, which subsequently reacted with 1-phenylbutadiene **127** in xylene at 145°C to give the PTFE-bound



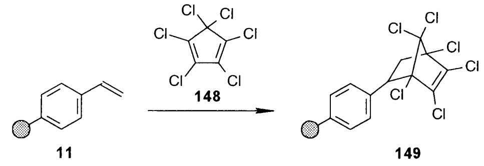
Scheme 35.



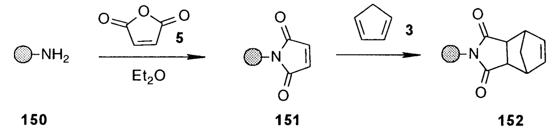
Scheme 36.



Scheme 37.



Scheme 38.

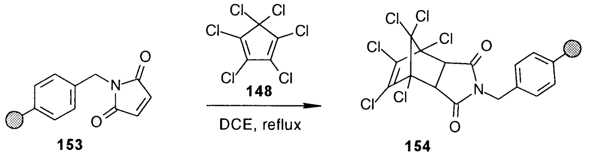


Scheme 39.

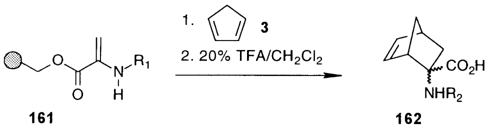
cycloadduct **144** as a mixture of *cis* and *trans* isomers (Scheme 36). The overall yield was 46% after cleavage with 95% TFA.

Winkler and McCoull[42] reported a stereoselective Diels–Alder reaction of the Merrifield resin-bound *N*-crotonyl oxazolidinone dienophile **145** with cyclopentadiene **3** in the presence of Et_2AlCl as a Lewis acid catalyst (Scheme 37). The solid-phase cycloaddition reaction provided the desired cycloadduct **146**. Lithium benzyloxide treatment of **146** to remove the Evans oxazolidinone auxiliary afforded **147** as a 21:1 mixture of *endo* and *exo* isomers with 86% ee in 26% overall yield. The analogous solution-phase cycloaddition reaction gave **147** as a >20:1 mixture of *endo* and *exo* isomers with 88% ee in 42% overall yield.

Stranix and Darling[11] found that vinylpolystyrene **11** can act as a dienophile in [4π+2π] cycloaddition reactions if an electron-poor diene such as hexachlorocyclopentadiene **148** is used. Hexachlorinated bicyclo[2.2.1]heptene **149** was obtained as a major product in good yield (Scheme 38).



Scheme 40.



Scheme 42.

Table 8. Preparation of carbocyclic amino acids

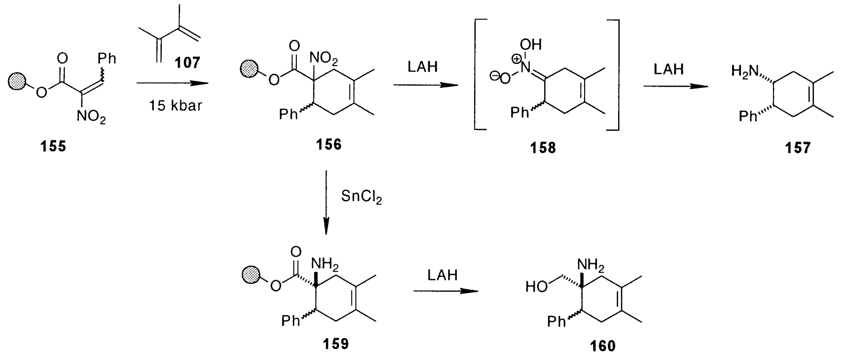
Compound	R_1 (**161**)	R_2 (**162**)	*endo*:*exo*	Yield (%)[a]
162a	CBZ	CBZ	1:4	73
162b	Ac	Ac	1:2	67
162c	BOC	H, TFA salt	1:4	72

[a] Yields are isolated yields, and are based on the loading of resin.

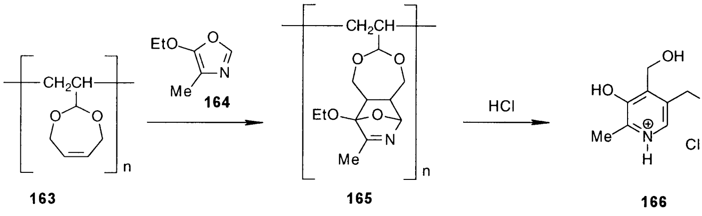
Maleimide has been immobilised to a solid support as a dienophile in two separate investigations of the intermolecular Diels–Alder reactions.[43,44] In the first study, Blazka and Harwood[43] allowed the macroreticular styrene-4-aminostyrene-divinylbenzene **150** to react with maleic anhydride **5** to yield the dienophilic resin **151** (Scheme 39). This was subsequently reacted with cyclopentadiene **3** to give the resin-bound cycloadduct **152** as indicated by the IR spectrum of the product. Later work by Hinch and Stevens[44] involved reacting maleimidomethylated polystyrene **153** with hexachlorocyclopentadiene **148** in refluxing 1,2-dichloroethane to prepare the chlorinated Diels–Alder adduct **154** for differential thermal analysis and flammability studies (Scheme 40).

Kuster and Scheeren[36] prepared various nitroalkenes on the Wang resin, and used them as follows in high pressure-promoted Diels–Alder reactions. The Diels–Alder reaction between **155** and 2,3-dimethylbutadiene **107** under a pressure of 15 kbar gave the cycloadduct **156** (Scheme 41). These authors used the traceless linker approach to prepare the cyclic phenylethylamine **157** via an *aci*-nitro intermediate **158** by using LAH as the reducing agent. It is important to note that only one diastereomer (**157**) was formed from the diastereomeric mixture of two cycloadducts **156**, due to the controlled hydride attack on **158**. In addition, cyclic phenylethylamino alcohols **160** can be prepared by two successive reduction reactions, initially by $SnCl_2$ giving **159** and then by LAH giving **160**.

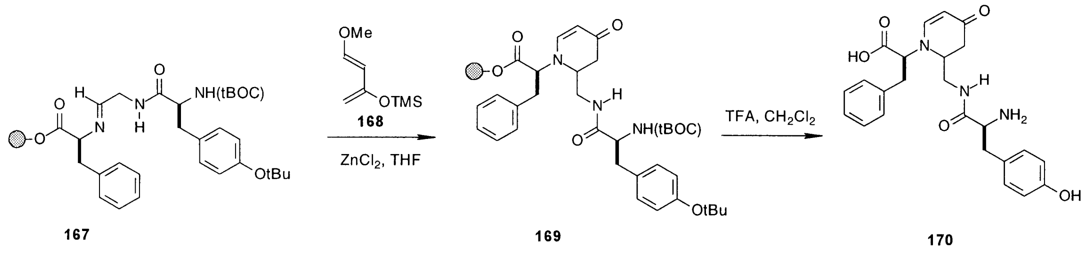
Burkett and Chai[45] have reported an interesting application of polymer-supported dehydroalanine derivatives in the



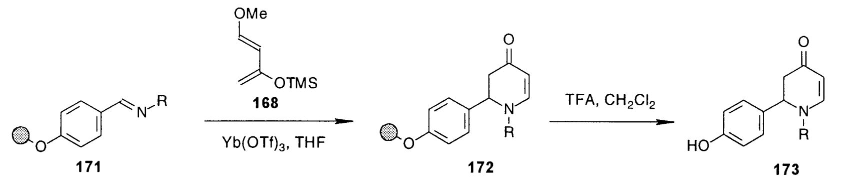
Scheme 41.



Scheme 43.



Scheme 44.

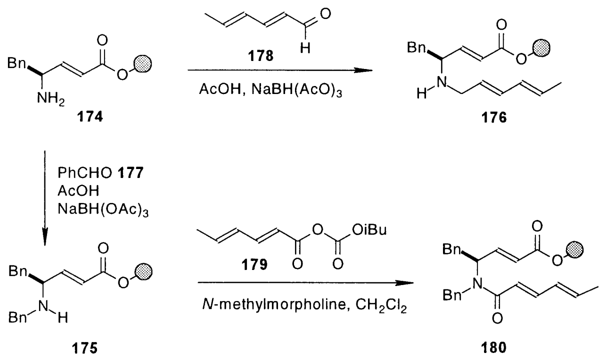


Scheme 45.

Diels–Alder reaction. The authors provide several synthetic routes for preparing Wang resin-bound dehydroalanines. The [4π+2π] cycloaddition reactions between the dehydroalanines **161** and cyclopentadiene **3** were carried out in toluene at 80°C (Scheme 42). The Diels–Alder adducts **162** were cleaved from the resin by TFA for the determination of the *endo*/*exo* selectivities (Table 8). The *endo*/*exo* selectivities obtained in the solid-phase reactions are in accord with the selectivities of the corresponding solution-phase reactions.

3.2. Hetero Diels–Alder reactions

Ritter and Sperber[46] synthesised pyridoxine (vitamin B_6) by a Diels–Alder reaction between the polymeric dienophile **163** and a heterocyclic diene, 5-ethoxy-4-methyloxazole **164**, in a sealed tube at 130°C (Scheme 43). The polymer support was prepared by condensing poly(vinylformal) and *cis*-2-butene-1,4-diol. The pyridoxine cycloadduct **166** was removed from the polymeric backbone **165** by acidic hydrolysis that gave poly(vinylformal) as a reusable side product.



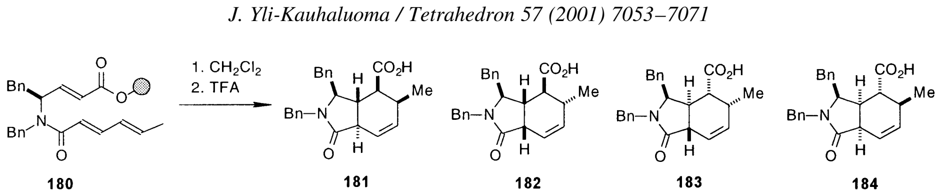
Scheme 46.

Goodman et al.[47] used the H–Phe-Wang resin-bound imine **167**, which reacted with the Danishefsky diene **168** in the presence of $ZnCl_2$ as a Lewis acid catalyst to give the resin-bound product **169** (Scheme 44). The pyridone **170** was obtained in 55% overall yield (de >95%) after deprotection and cleavage from the resin by TFA. A similar Diels–Alder type reaction has been utilised in the solid-phase preparation of pyridopyrazine opioids.

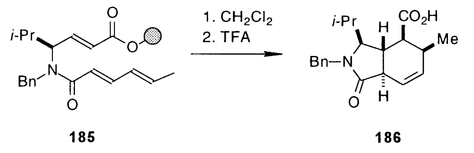
Wang and Wilson[48] report the use of *p*-hydroxybenzaldehyde-modified Wang resin in the trimethyl orthoformate-assisted preparation of imines, and their formal hetero Diels–Alder reactions with Danishefsky's diene (Scheme 45). The resin-bound imines **171** (R=Bu, *i*-Bu, *i*-Pr, Bn, Ph, 4-MeOPh, cyclopentyl, cycloheptyl) reacted with Danishefsky's diene **168** in the presence of various Lewis acids, the water-tolerant $Yb(OTf)_3$ giving the best yields of resin-bound 2,3-dihydro-4-pyridones **172**. Cleavage of **172** with 50% TFA in CH_2Cl_2 gave **173** in good yields. This formal Diels–Alder reaction is presumed to proceed by a tandem Mannich–Michael mechanism.

4. Intramolecular Diels–Alder reactions

Sun and Murray[49] investigated several intramolecular



Scheme 47.



Scheme 48.

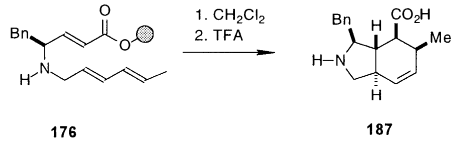
solid-phase Diels–Alder reactions of amino acid trienes. These reactions gave highly functionalised hydroisoindole derivatives. The starting materials were conveniently prepared by the solid-phase olefination reaction between diethylphosphonoacetyl Wang resin and various FMOC-protected amino aldehydes. Removal of the FMOC group afforded the primary amines **174** that were reductively alkylated to **175** and **176** using benzaldehyde **177** or 2,4-hexadienal **178**, respectively (Scheme 46). The resin-bound amine **175** was acylated with isobutyl chloroformate-activated 2,4-hexadienoic acid **179** to give the resin-bound triene **180**. The intramolecular Diels–Alder reaction of **180** in CH_2Cl_2 went to completion at room temperature (Scheme 47). After cleavage with 20% TFA in CH_2Cl_2, an isomer ratio of 10:10:3:1 was obtained from a reverse-phase HPLC assay. According to the ^1H NMR assignment, the structures **181** and **183** represent the two major isomers, the total yield of **181** and **183** being 38%. When the resin-bound triene **185** underwent the intramolecular cycloaddition reaction, however, the major isomer was found to be **186**, the amount of minor isomers was <10% by ^1H NMR, and the cycloadduct **186** was obtained in 48% yield (Scheme 48).

The [4π+2π] cycloaddition product **187** was obtained from the intramolecular reaction of the triene **176** in CH_2Cl_2 at room temperature. After TFA cleavage, the cycloadduct **187** was isolated as the sole product in 55% yield (Scheme 49). According to the authors, the diastereoselectivity of the solid-phase cycloaddition reactions resembles that of the correspondent solution-phase reactions. The favoured reaction pathway traverses through the *endo* transition-state, and the steric bulk of the γ-substituent affects the 1,3-allylic interaction of the dienophilic part of the triene.[49]

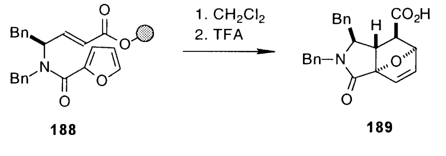
The same authors studied the intramolecular solid-phase Diels–Alder reaction of trienes containing a furan ring moiety, which has been found to be a useful auxiliary in the synthesis of functionalised heterocyclic compounds. The resin-bound furoic amide triene **188** underwent the intramolecular Diels–Alder reaction at room temperature to produce the epoxyhydroisoindoline **189** in 55% yield (Scheme 50). All of the intramolecular cycloaddition reactions of furan-substituted trienes which were studied followed the *endo* route.

Finally, Sun and Murray[49] investigated the solid-phase intramolecular Diels–Alder reaction of the vinylfuran derivative **190** (Scheme 51). The reaction of triene **190** went to completion in CH_2Cl_2 at room temperature for 2 days. The intramolecular Diels–Alder reaction was followed by an aromatisation reaction to afford the *trans*-fused tricyclic product **191** in 37% yield.[49]

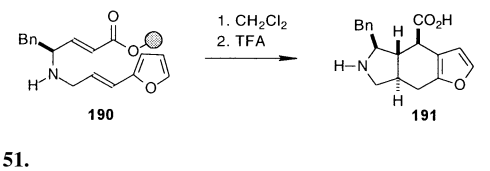
Recently, Murray et al.[50] have reported the use of vinylbenzenes and their substituted derivatives as dienes in solid-phase intramolecular Diels–Alder reactions. An intramolecular cycloaddition reaction of the resin-bound *p*-nitro-substituted vinylbenzene **192** gave **193** as the only observed cycloadduct (Scheme 52). Although the dienoic and dienophilic parts of **192** are both electron-deficient, its intramolecular Diels–Alder reaction proceeded as smoothly as the corresponding reactions of the electron-rich vinylbenzenes. The dipole repulsion of the dienoic and dienophilic portions did not affect the reactivity of vinylbenzenes, yet it seems to have had a favourable effect on the stereoselectivity of the cycloaddition reaction. On the other hand, the intramolecular cycloaddition reactions of the vinylbenzenes with complementary dienoic and dienophilic segments displayed reduced diastereoselectivity and less clean reaction products.



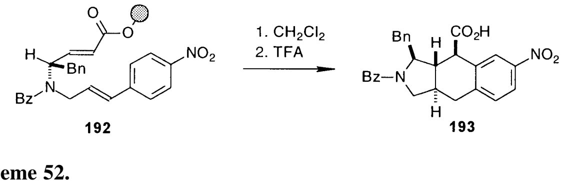
Scheme 49.



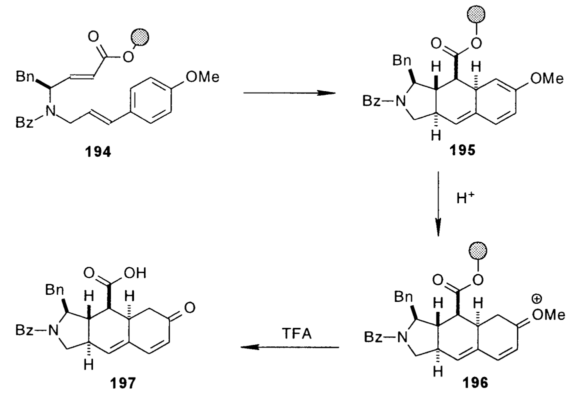
Scheme 50.



Scheme 51.

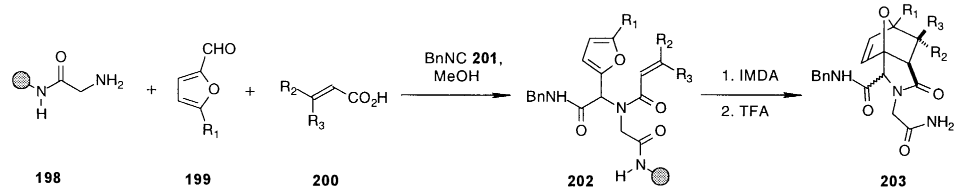


Scheme 52.



Scheme 53.

A highly efficient four-component condensation/intramolecular Diels–Alder reaction was adapted to solid support by Paulvannan (Scheme 54).[51] Glycine-functionalised acid-labile ArgoGel-Rink resin **198** was condensed with a 10-fold excess of furaldehyde **199**, the maleic or fumaric acid derivative **200** and benzyl isocyanide **201** to give the triene **202** in a Ugi reaction. The triene **202** underwent a spontaneous intramolecular Diels–Alder reaction to produce the lactam **203** as a mixture of isomers in high yield (Table 9). This type of a tandem four-component condensation/intramolecular Diels–Alder reaction enables the preparation of tricyclic lactam libraries with a high degree of diversity, since a wide range of structurally unique primary amines, aldehydes, furaldehydes, and isonitriles are commercially available. Schreiber et al.[52,53] have utilised these four-component Ugi reactions, intramolecular Diels–Alder reactions, and additional ring-opening-closing olefin metathesis reactions as a complexity-generating cascade for providing structurally diverse compounds in the solid phase.



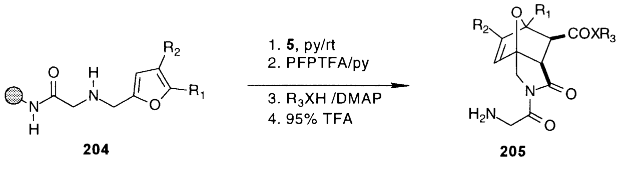
Scheme 54.

Table 9. Tandem four-component condensation/intramolecular Diels–Alder reaction

Compound	R_1	R_2	R_3	Isomer ratio	Yield[a] (%)
203a	H	CO_2Et	H	91:9	95
203b	H	H	CO_2Et	89:11	92
203c	H	H	CONHBn	88:12	88
203d	Me	CO_2Et	H	78:22	95
203e	Me	H	CO_2Et	77:23	88
203f	Me	H	CONHBn	88:12	92

[a] Yields are isolated yields, and are based on the loading of resin.

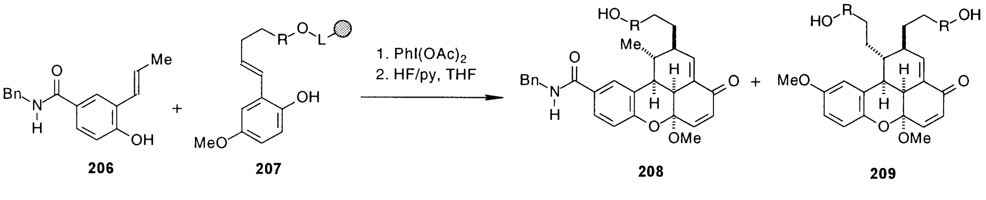
The electron-rich *p*-methoxy-substituted vinylbenzene **194** reacted rapidly in the intramolecular cycloaddition reaction at room temperature (Scheme 53). Upon treatment with TFA, the intermediate **195** was suggested to participate in an acid-catalysed demethylation reaction, affording the tricyclic compound **197** in 27% yield.[50]



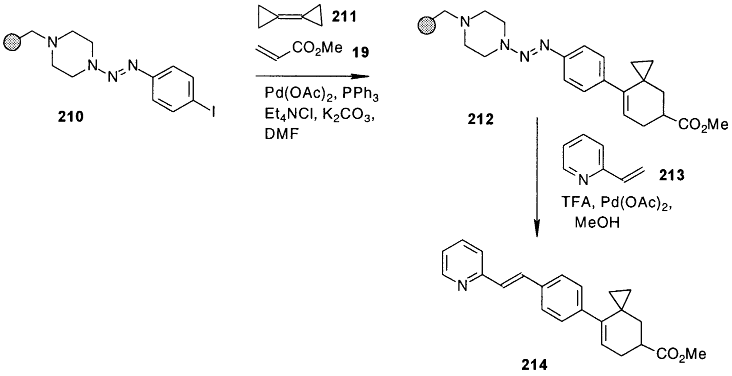
Scheme 55.

Paulvannan et al.[54] have reported the preparation of heterotricycles via an intramolecular Diels–Alder reaction of substituted furans (Scheme 55). As these authors wished to prepare a large number of diverse tricyclic nitrogen-containing heterocycles, they embarked upon the preparation of cycloadducts, the carboxyl group of which could be elaborated to ester and amide functionalities. The cycloadduct **205** (X=NH or O) was prepared by allowing the resin-bound diene **204** to react with maleic anhydride **5** in pyridine through an initial *N*-acylation, and a subsequent [4π+2π] cycloaddition reaction. Pentafluorophenyl trifluoroacetate activation of the carboxyl group was employed prior to its reactions with various amines and alcohols to provide amides and esters, respectively. The cycloaddition reactions were found to consistently proceed in high yields (>90%).

Shair et al.[55] investigated a biomimetic solid-phase synthesis of carpanone derivatives. The authors studied the effect of a linker on the ratio of the hetero- and homo-coupling products arising from the *endo*-selective inverse



Scheme 56.



Scheme 57.

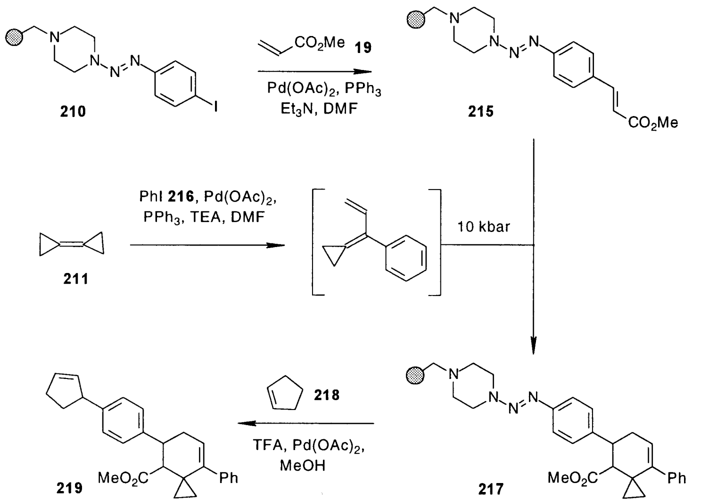
electron demand Diels–Alder reaction between the electron-deficient dienophilic phenol **206** and the electron-rich phenolic diene **207** (Scheme 56). A ratio of 5.3:1 for **208**:**209** was observed when an amide linker (L=–$Si(Et)_2$–; R=–$[CH_2CONH]_2CH_2CH_2$–) was used. The inverse electron demand Diels–Alder reaction proceeds with complete control of stereochemistry as **208** was isolated as a single isomer. (Diacetoxyiodo)benzene-assisted oxidative heterocoupling of **206** and the resin-bound **207** gave **208**, while **209** was obtained from the intra-bead homocoupling of **207**. The authors note that all other oxidants that were tested gave only the homocoupled product **209**. Intrabead coupling was diminished when an amide linker was used instead of the silyl or trityl linkers. The authors provided several additional examples of these biomimetic solid-phase reactions in their paper.

5. Miscellaneous polymer-supported Diels–Alder reactions

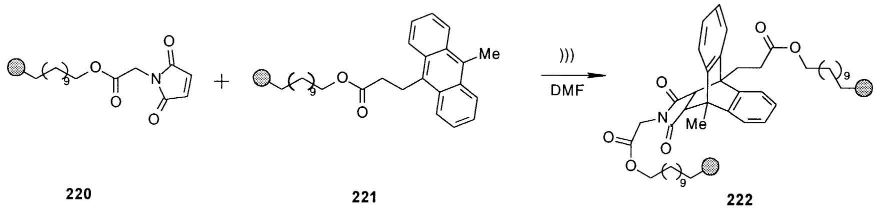
Recently, de Meijere et al.[56] have used an intriguing domino Heck–Diels–Alder reaction to obtain a polystyrene-bound triazaphenyl-substituted spiro[2.5]octene (Scheme 57). Merrifield resin-bound triazenylphenyl iodide **210** was allowed to react with bicyclopropylidene **211** and methyl acrylate **19** to afford cycloadduct **212** in the presence of palladium acetate and triphenylphosphine in DMF. This type of solid-phase reaction is especially favourable, since the tendency of iodoarenes to dimerise is reduced, and the bicyclopropylidene dimer byproducts are easy to remove by filtration. The Heck cycloadduct **212** was subjected to a further Heck reaction with 2-ethenylpyridine **213** to provide the (*E*)-2-pyridylethen-2-yl phenylspiro[2.5]octene **214** in 55% yield.

The same authors additionally studied various permutations of the Heck–Diels–Alder sequence.[56] They first coupled the polystyrene-bound triazenylphenyl iodide **210** with methyl acrylate **19** in a Heck reaction, and then introduced the Heck product **215** in the domino Heck–Diels–Alder reaction sequence with bicyclopropylidene **211** and iodobenzene **216** to give the resin-bound **217** (Scheme 58). Two steps were required to perform this novel, five-component Heck–Heck–Diels–Alder reaction. Finally, the cycloadduct **217** was subjected to Heck conditions in the presence of cyclopentene **218** to produce spiro[2.5]octene **219** in 51% yield. According to the authors, the versatility of this reaction sequence in combinatorial chemistry lies both in the variability of the starting materials, and in the diversity of different combinations of Heck/Diels–Alder reactions.

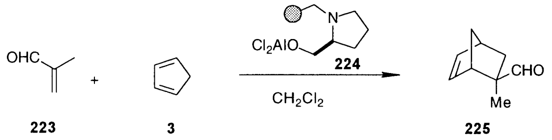
An unusual covalent adhesion of the dienophilic *N*-(carbonylmethyl)maleimide-functionalised polystyrene **220** to the



Scheme 58.



Scheme 59.



Scheme 60.

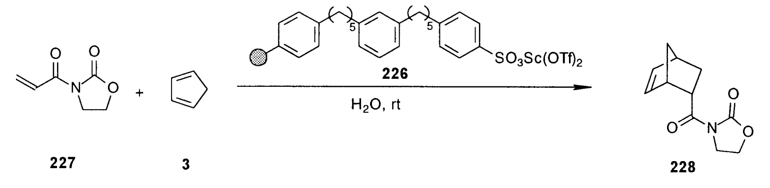
dienoic 9-(2-carbonylethyl)-10-methylanthracene-functionalised polystyrene **221** through an inter-bead Diels–Alder reaction was reported by Thomas et al.[57] (Scheme 59). They observed the aggregation phenomena of the functionalised beads after sonication and centrifugation in DMF. For monitoring purposes, the diene beads **221** were stained with a dienophilic dye, Disperse Red, to give a bright red colour prior to sonication and reaction with the maleimide resin **220**. The inter-bead Diels–Alder reaction of the stained diene beads **221** with the dienophile beads **220** was monitored by observing the aggregation of the cycloadduct beads **222** by microscopy after dispersal of the beads in water. The current interpretation of these experiments is a [4π+2π] cycloaddition reaction occurring between the resin-bound diene **221** and the immobilised dienophile **220** on separate beads.

6. Polymer-supported catalysts for the Diels–Alder reaction

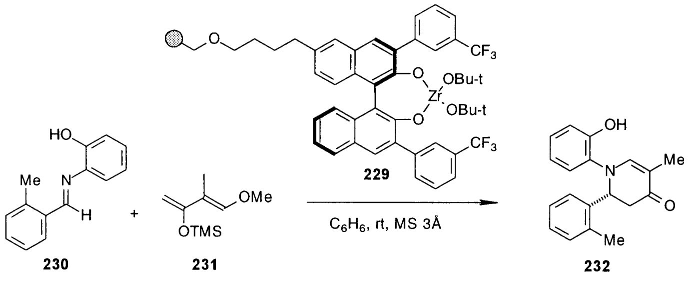
Luis et al.[58] prepared polymer-supported aluminium catalysts for Diels–Alder reactions, and studied the effect of the polymer backbone and its coordinating atoms on the selectivity of the reaction (Scheme 60). The Diels–Alder reaction between methacrolein **223** and cyclopentadiene **3** in CH_2Cl_2 at −30°C in the presence of various polymer-supported prolinol–aluminium Lewis acids was extensively studied. In the presence of the catalyst **224**, for example, the *exo* cycloadduct **225** was obtained, the ee of the reaction being 25%, the highest in this study. The *endo*/*exo* selectivity remained fairly constant, independent of the structure of the polymeric backbone of the Lewis acid catalyst.

Finally, two examples of the use of a solid-supported chiral zirconium catalyst and water-tolerant scandium catalyst have been reported. Nagayama and Kobayashi[59] prepared the polystyrene-bound scandium trifluoromethanesulfonate **226**, and used it as a Lewis acid catalyst in the Diels–Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one **227** and cyclopentadiene **3** to afford **228** in quantitative yield with an *endo*/*exo* ratio of 92:8 (Scheme 61), only 1.6 mol% of **226** being used in the cycloaddition reaction. This type of polymer-supported Lewis acid catalyst is likely to find many applications, since it tolerates water, is easily recovered, and can be reused.

Recently, Kobayashi et al.[60] have developed effective polymer-supported zirconium (*R*)-1,1′-binaphthol catalysts for asymmetric aza Diels–Alder reactions. The zirconium BINOL **229** catalysed the cycloaddition reaction between aldimine **230** and Danishefsky's diene **231** in benzene at room temperature producing **232** in 99% yield, and with an ee of 91% (Scheme 62).



Scheme 61.



Scheme 62.

7. Summary and outlook

The pericyclic Diels–Alder reactions are synthetically versatile for the efficient formation of two carbon–carbon bonds. Due to their consistently high regioselectivity, diastereoselectivity and enantioselectivity, the Diels–Alder reactions have been used in numerous instances to prepare substituted cyclohexene-type structures. Recently, Diels–Alder reactions have also been performed in solid supports. This review of the literature encompassing the reactions up to June 2000 has described several reports on both intermolecular and intramolecular Diels–Alder reactions (normal and inverse electron demand reactions). Some examples of the hetero Diels–Alder reactions have additionally been published. There are, however, no reports to date, for example, on enyne cycloaddition reactions on solid supports. Further work on the solid-supported Diels–Alder reactions, and especially in the hitherto unexplored areas of $[4\pi+2\pi]$ cycloaddition reactions, is certain to provide fascinating new applications in the future.

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