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Review

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Asymmetric and Diastereoselective Conjugate Addition Reactions: C−C Bond Formation at Large Scale

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ABSTRACT: Asymmetric and diastereoselective conjugate addition reactions are discussed from an industrial perspective including examples of (1) Lewis acid/Brønsted base catalysis, (2) phase transfer catalysis, (3) organocatalysis, and (4) transition metal/ligand catalysis with organometallic reagents.

1. INTRODUCTION

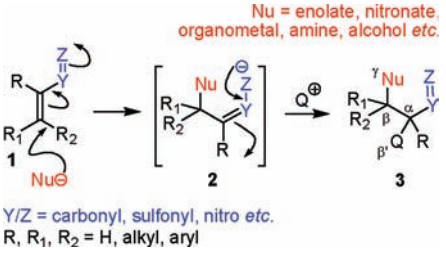
In the field of asymmetric synthesis and indeed all areas of synthetic organic chemistry, only a fraction of the available literature procedures is ever demonstrated at industrially significant (mole or kilogram) scale.[1] Many literature methods are unsuitable for scale-up due to a failure to satisfy one or more of the following criteria:[2]

Safety considerations (avoidance of potentially hazardous materials and processes)
Environmental concerns (e.g., solvent and waste-stream or gas-emission restrictions)
Legal aspects (freedom to operate)
Economical constraints (cost of materials and processing)
Control requirements (reproducibility, robustness, product purity)
Throughput (amount of material generated per unit time)

Another pertinent observation is that many of the available asymmetric methodologies, whilst displaying fantastic selectivity and efficiency, generate products or structural motifs that are not (currently) of industrial interest.

One area of asymmetric synthesis that has attracted particular interest over the last 10−15 years is the stereocontrolled addition of various nucleophiles to activated olefins (Scheme 1). This can be termed "Asymmetric Conjugate Addition" (ACA) when new stereogenic centres are generated from prochiral substrates or "Diastereoselective Conjugate Addition" (DCA) where chiral, nonracemic substrates are used to control new stereochemical information. Although perhaps not as well developed as other areas of asymmetric synthesis (hydrogenation, epoxidation, Aldol/Mannich-type reactions), an impressive range of high-performing protocols can be found to promote ACA or DCA between various carbon nucleophiles (e.g., enolates, nitronates, organometallics) and α,β-unsaturated electrophiles (e.g., α,β-unsaturated carbonyls, nitriles, sulfones, and nitroalkenes). In these reactions, stereocontrol has been demonstrated in a number of ways such as substrate or auxiliary control (DCA) and varying forms of catalysis (ACA; transition metal catalysis, organocatalysis, phase-transfer catalysis). Depending on the substitution pattern of the α,β-unsaturated electrophile (**1**, Scheme 1), it is possible to form one (typically at the β-position) or two (α- and β-positions) new stereocentres; if the nucleophile is *prochiral*, it is possible to generate a third stereocentre (γ), and if the intermediate enolate-type species is intercepted with a suitable electrophile Q (carbon-centred as opposed to a proton source), generation of a further stereocentre is possible (β'). Despite the obvious power of this type of reaction, the number of said ACA or DCA procedures that have been demonstrated at kilogram or even multigram scale remains limited. It should, however, be expected that, as this area of synthetic chemistry evolves and matures in the coming years, more of these inventive and novel procedures will see industrial application.

Scheme 1. Conjugate addition



Conjugate Addition is a very general topic for discussion and this review will only cover the use of *carbon* nucleophiles (i.e., C−C bond formation); the topic of heteroatom nucleophiles (e.g., C−N, C−O formation) will be covered in a subsequent review. Two general subtopics are considered herein: i) the addition of active C−H ("stabilised" or "soft") nucleophiles, commonly known as Michael addition,[3] and ii) the addition of organometallic ("non-stabilised" or "hard") nucleophiles. Each subtopic will include examples of substrate-control (diastereoselective synthesis including auxiliary-based approaches) and asymmetric catalysis.

This review will focus on large-scale ACA and DCA, typically considering reactions of hundreds of grams or larger. Smaller-scale examples will also be discussed where the *potential* for scale-up is clear. Assessment of scale-up potential is obviously very subjective, and the SELECT criteria are used as a guideline. In broader terms, the requirements for, e.g., argon

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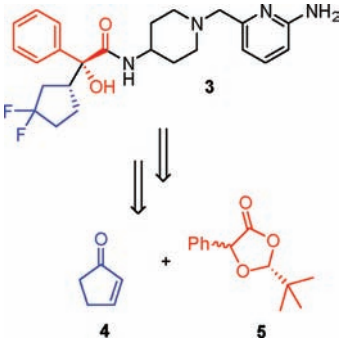
atmospheres, highly complex catalysts, or explosive or highly toxic reagents are likely to render a process nonscaleable.

2. ADDITION OF STABILISED, ACTIVE C−H NUCLEOPHILES (MICHAEL ADDITION)

This type of reaction, where a stabilised, "soft" carbon nucleophile is added to an α,β-unsaturated electrophile (traditionally known as the Michael reaction)[3] represents a major subsection of the conjugate addition class of transformations. The ability to construct carbon−carbon bonds (and associated stereocentres) under often mild conditions makes this reaction particularly amenable to all types (and scales) of application. Within this class of reaction, stereocontrol has been demonstrated using various techniques such as simple (diastereoselective) substrate control, auxiliary-based approaches (also diastereoselective), transition metal catalysis, organocatalysis, phase transfer catalysis, etc.

2.1. Diastereoselective Conjugate Addition (DCA). The coupling of a lithium (or other metal) enolate with an α,β-unsaturated enone under kinetic control represents one of the earliest examples of large-scale Michael reaction. Seminal studies in the 1980s by Heathcock et al. had already highlighted the complexity and subtleties of stereocontrol in this type of reaction.[4] This series of papers on acyclic stereocontrol highlighted the effects that parameters such as enolate geometry, counterion, and sterics can have on regioselectivity (1,2- versus 1,4-selectivity) and stereoselectivity (diastereoselectivity). Many of these observations proved pertinent to the following example from 2001. Scientists from Banyu and Merck described the synthesis of M_3 muscarinic antagonist **3** (Scheme 2), a drug candidate for the treatment of chronic obstructive

Scheme 2. Muscarinic acid synthesis via Michael addition



pulmonary diseases and urinary incontinence.[5] Acetal **5** was synthesised at multikilo scale from mandelic acid and pivaldehyde and subsequently reacted with cyclopentenone **4** under a range of Michael- and Mukaiyama−Michael-type conditions (Table 1).

In all cases, the auxiliary efficiently promoted *Re*-facial selectivity at the enolate terminus (less than 10% **9** in all cases); stereocontrol at the adjacent tertiary centre was less impressive. Simple alkali metal and zirconium enolates (entries 1−4) favored the undesired diastereomer **8**, whilst Mukaiyama−Michael-type reactions (utilising silyl enol ethers, entries 8−11) did favor the desired diastereomer **7**, albeit with disappointing levels of stereocontrol. The zinc enolate (entry 7) gave the most promising results, reacting faster and more selectively than the parent lithium enolate and crucially favoring the desired stereoisomer **7**. Significant optimisation studies showed that solvent composition was critical and selectivity could be dramatically increased through addition of the relatively cheap 1-(2-dimethylaminoethyl)-4-methylpiperazine ligand **10a**. Kinetic studies showed that, in the presence of **10a**, the zinc enolate reacted 7−10 times faster than the parent lithium enolate. This allowed for a substoichiometric loading of metal ($ZnCl_2$; 15 mol %), resulting in a 25-kg, catalytic process as outlined in Scheme 3. Although requiring a complicated solvent system and cryogenic temperatures, this example is impressive in that two adjacent stereocentres are constructed (one of which is quaternary) and a sterically congested tetra-substituted enolate is reacted with complete conversion and little or no competing 1,2-addition.

A similar, auxiliary-based approach was described by scientists from Pfizer between 1993 and 2003.[6] As part of their hypertension drug programme, a pair of geminal-cycloalkylglutaramide derivatives (candoxatrilat and sampatrilat, Figure 1) were synthesised via Michael addition reaction of the key Bayliss−Hillman adduct **11** with cyclopentanecarboxylic acid **12** (Scheme 4). In both cases, a new stereocentre was generated at the α-position in **13** via diastereoselective protonation of the initial enolate products; stereocontrol was exerted with the use of (*S*,*S*)-bis(α-methylbenzyl)amine auxiliaries. As a point of interest, after preliminary modelling experiments, it was postulated that diastereoselective enolate protonation occurred from the front face of either of the two preferred conformers (**14** and **15**; Scheme 4) which were both predicted to be of low energy.

Scale-up synthesis of sampatrilat was described using a seemingly robust and reliable process (Scheme 4). Reaction volumes were kept relatively low, plant-friendly reaction temperatures were found to be suitable, and provided the input Michael substrate **11** was of high purity, yields and stereoselectivities proved repeatable at 2-kg scale.

The use of chiral auxiliaries proved effective for large-scale Michael addition reactions in the examples above, but this approach suffers the inherent drawback of requiring stoichiometric levels of stereochemical information. More recently a range of substoichiometric (asymmetric catalytic) methods have also been demonstrated at large scale; these will be discussed in the following section.

2.2. Michael Addition (ACA) using Lewis Acid/Brønsted Base Catalysis. Metal catalysts have been utilised in a number of large-scale Michael processes to good effect. One approach that has proven successful is the reaction of nitroolefins with chiral enolates which are generated catalytically from 1,3-dicarbonyls using chiral Lewis acids and Brønsted bases (Scheme 5). The combination of readily enolisable 1,3-dicarbonyls and strongly electron-deficient nitroolefins means that relatively mild Lewis acids and Brønsted bases can be used under ambient conditions which are particularly suited to larger-scale processes.

The following example from Abbott gives a rigorous account of a somewhat unusual magnesium-catalysed Michael reaction.[7] In addition to completing general process development and scale-up activities, particular attention was paid to the active catalyst species, the reaction mechanism, and also the reaction kinetics. The findings serve as clear examples of not only the synthetic power but also the potential subtleties and difficulties associated with metal-mediated asymmetric catalysis at large scale.

ABT-546 (Scheme 6), an endothelin antagonist, was highlighted as a possible treatment for cancer and congestive

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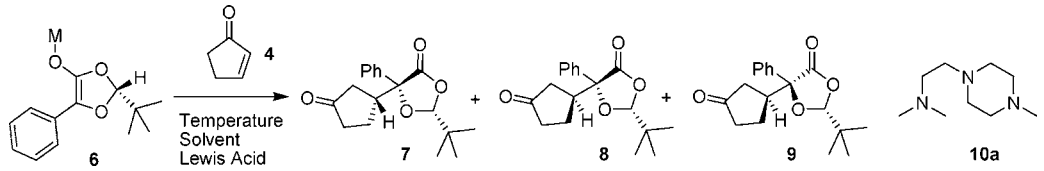
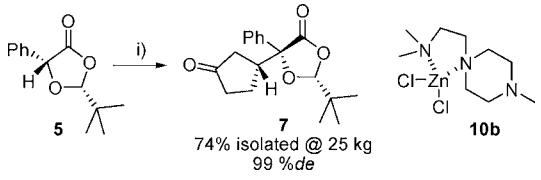
Table 1. Screening of Lewis acids for Michael addition



entry[a]	metal (M)	Lewis acid	solvent	7:8[b]	yield (%)[b]
1	Li	–	THF	1:1.5	89
2	Na	–	THF	1:2	92
3	K	–	THF/toluene	1:2.5	92
4	Li	$ZrCl_4$[c]	THF	1:3.2	90
5	Li	Cp_2ZrCl_2	THF	2.8:1	88
6	Li	Cp_2TiCl_2	THF	1.5:1	90
7	Li	$ZnCl_2$	THF	3:1	75
8	TBS[d]	$TiCl_4$[e]	DCM	2.1:1	93
9[f]	TBS	Cp_2ZrCl_2	DCM	1.9:1	21
10	TBS	$ZrCl_4$	THF	1.9:1	98
11	TBS	$ZrCl_4$	DCM	1.3:1	93

[a]All reactions were carried out at −78 °C unless otherwise stated. [b]Ratios and yields were determined by HPLC. [c]Metal enolates were prepared from the lithium enolate by addition of 1.2 equiv of a suitable metal salt. [d]The *tert*-butyl dimethylsilyl (TBS) derivatives were generated from the lithium enolate in THF by addition of TBS-Cl; the corresponding TMS derivatives were also prepared and gave similar results. [e]The enone and Lewis acid were premixed in an appropriate solvent at the reaction temperature then added to a solution of preformed silyl enol ether. [f]The reaction was carried out at 25 °C.

Scheme 3. Muscarinic antagonist synthesis[a]



[a]Reagents and conditions: i) LDA (1.2 equiv), **10a** (4 equiv), **5** (1.0 equiv), 1,2-dimethoxyethane (15 vol), −15 °C, 15 min then **10b** (preformed; 15 mol %), toluene (16 vol), 0 °C, 1 h then **4** (1.2 equiv), toluene (1.5 vol), −78 °C, 50 min before acid quench and aqueous workup.

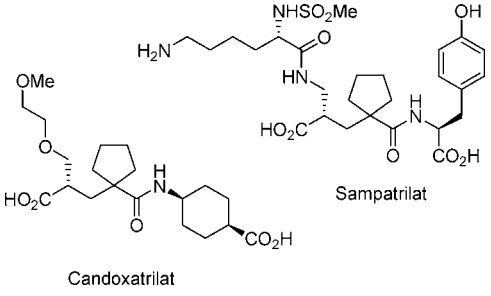
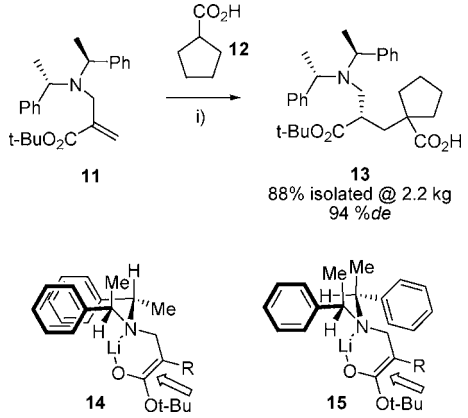


Figure 1. Neutral endopeptidase inhibitors.

heart failure; the ensuing development programme resulted in a novel example of magnesium catalysis for a 3-kg, asymmetric Michael reaction between *β*-ketoester **16** and nitroolefin **17**. Initial screening of metal/ligand combinations as well as chiral auxiliaries proved unsuccessful. Eventually, moderate (though variable) stereoselectivity was obtained by combining Mg(OTf)$_2$ with bisoxazoline (BOX) ligand **19** in ethanol/chloroform. Further studies showed that addition of an external Brønsted base (amine) cocatalyst greatly increased the rate of reaction; *N*-methylmorpholine (NMM) was eventually selected (1:1 loading w.r.t. metal catalyst). On the basis of this

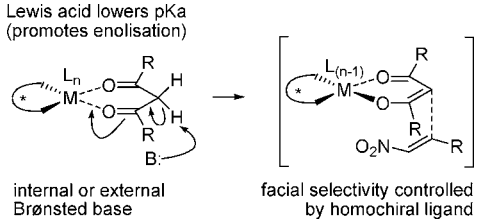
Scheme 4. Michael addition with enantioselective protonation[a]



[a]Reagents and conditions: i) LDA (2.2 equiv; 28 wt % in heptane), **12** (1.1 equiv), THF −30 to 20 °C, 16 h then **11** (1.0 equiv) in hexane (approx 4 vol), −10 °C, 80 min then citric acid (2 M, 4 vol), −15 °C to RT.

dependency for amine bases, a soft-enolisation mechanism was proposed as depicted earlier (Scheme 5). It should be noted that the reaction was found to be essentially non-diastereoselective in all cases (1:1 mixture of *syn*- and *anti*-**18**),

Scheme 5. Lewis acid/Brønsted base activation



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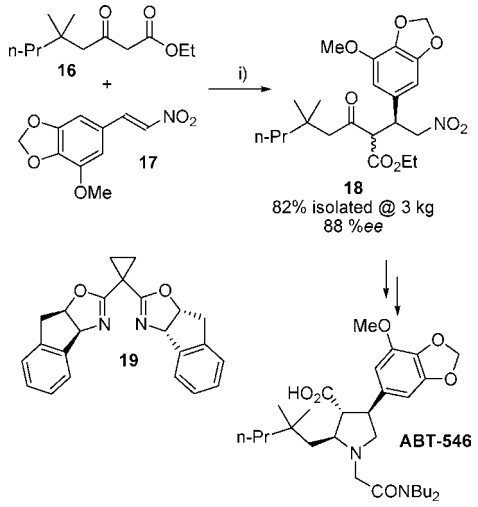
Scheme 6. Asymmetric Michael addition under magnesium-BOX Catalysis[a]



[a]Conditions and reagents: i) $Mg(OTf)_2$ (4 mol % hydrated with 16 mol % water), **19** (4.4 mol %), $CHCl_3$ (ethanol stabilised, 22 vol), RT, 1 h then 4 Å MS until dry, then **16** (1.2 equiv), **17** (1.0 equiv), NMM (5.5 mol %), 37 °C, 17 h.

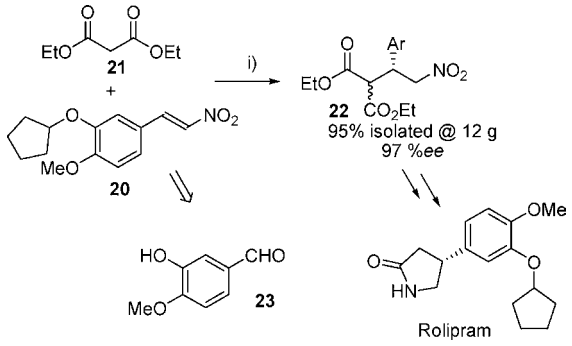
but facile epimerization of the α-stereocentre was demonstrated in the ensuing synthesis. Other reaction parameters were optimised, such as solvent (toluene and chloroform gave the best results but solubility issues arose with the former), metal counterion (triflate proved optimal) and ligand structure (all variations in the structure of **19** resulted in attenuation of selectivity).

Perhaps the most interesting observation, and one that epitomises the difficulties that can arise when using low-loading asymmetric catalysis, was the sensitivity of the reaction towards polar-protic contaminants. It was found that residual acetic acid present in the nitroolefin substrate **17** greatly inhibited reaction rate and the analogous β-ketocarboxylic acid of **16** (a trace impurity) was a stoichiometric poison to the catalyst. Moreover, sensitivity to water was even more pronounced; it was found that the active catalytic species only formed successfully in the presence of 4 equiv of water (w.r.t. Mg) but that the water then had to be removed from the system (using sieves) prior to reaction to promote the highest levels of conversion and selectivity. A reason for this phenomenon is suggested; water is required in the initial catalyst-forming step to prevent aggregation, which results in formation of an inactive catalyst.

The scope and generality were further studied, and it was demonstrated that nitroolefin electrophiles **20** could be reacted with other β-ketoester nucleophiles as well as synthetically versatile malonates **21** under similar reaction conditions. This was exemplified by the multigram synthesis of the anti-depressant rolipram (Scheme 7).

Nitroolefin **20** was generated from commercially available isovanillin **23**, and the ensuing asymmetric Michael addition with diethylmalonate **21** proceeded with excellent yield and selectivity. Further derivatisation of the Michael adduct gave rolipram in a total of six steps with excellent overall yield. The use of magnesium in the example above is preferable to many other metal catalysts since toxicity issues are negated;[8] the apparent dependence for solvents such as chloroform does, however, raise toxicological and environmental issues.

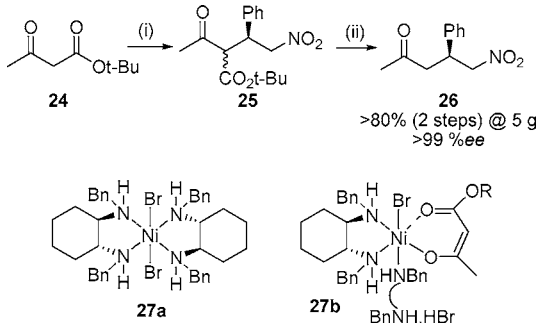
Scheme 7. Synthesis of rolipram[a]



[a]Reagents and conditions: i) $Mg(OTf)_2$ (5 mol % hydrated with 20 mol % water), *ent*-**19** (5.5 mol %), $CHCl_3$ (10 vol), RT, 30 min then 4 Å MS sieves, RT, 30 min then **20** (1.0 equiv), **21** (1.2 equiv), $CHCl_3$ (15 vol), *N*-methylmorpholine (6 mol %), RT.

Alternative metal-catalysed systems have been reported for similar, gram-scale asymmetric Michael reactions between malonates and nitroolefins. Evans et al. described a seemingly scaleable nickel-catalysed protocol that required exceptionally low catalyst loading and ambient temperatures (Scheme 8).[9]

Scheme 8. Asymmetric Michael addition using nickel catalysis[a]



[a]Reagents and conditions: (i) **24** (1.2 equiv), nitrostyrene (1.0 equiv), **27a** (0.01 mol %), toluene (2 vol), RT, 36 h; (ii) TsOH, benzene, reflux, 2 h.

Whilst the use of nickel catalyst **27a** might cause difficulties for pharmaceutical applications,[10] the very low loading used makes this protocol viable for larger-scale use.

Various β-ketoester and malonate substrates were tested, and the observed yields and enantioselectivities were uniformly high. Diastereoselectivity was typically low, but since the stereocentre in question (**25**) is part of a 1,3-dicarbonyl system, the opportunity to epimerise or decarboxylate (as in Scheme 8) is important. The mechanistic pathway is postulated to be similar to that in the previous example (Scheme 5). Complexation of **24** to **27a** causes partial decomplexation of one diamine ligand which then deprotonates *internally* to give a species such as **27b**.

Other bifunctional Lewis acid/Brønsted base catalysts of the type developed by Shibisaki have also been utilised for Michael reactions. The aluminium–lithium-BINOL (ALB) catalyst **31** depicted in Scheme 9 was employed at very low loading to effect the addition of dimethylmalonate **28** to cyclohexanone **29** at kilogram scale.[11] The Michael adduct **30** was a key starting material in the synthesis of (−)-strychnine, and the

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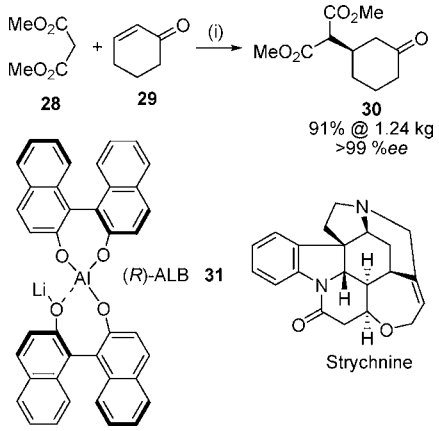
Scheme 9. Bimetallic catalysis[a]



[a]Reagents and conditions: (i) **28** (1.0 equiv), **29** (1.0 equiv), **31** (0.1 mol %), ^{t}BuOK (0.09 mol %), 4 Å MS sieves (10 wt %), THF, RT, 24 h.

ability to access kilogram quantities was vital to the total synthesis activity. This protocol is industrially amenable since the catalyst loading is very low, the two metal centres (Al, Li) are of minimal toxicity risk, and the reaction proceeds in a benign solvent (THF) and at ambient temperature. Indeed, application of this chemistry (**28** + **29** → **30**) was demonstrated by scientists at Actelion Pharmaceuticals at 7-kg scale during the synthesis of an undisclosed pharmaceutical compound.[12]

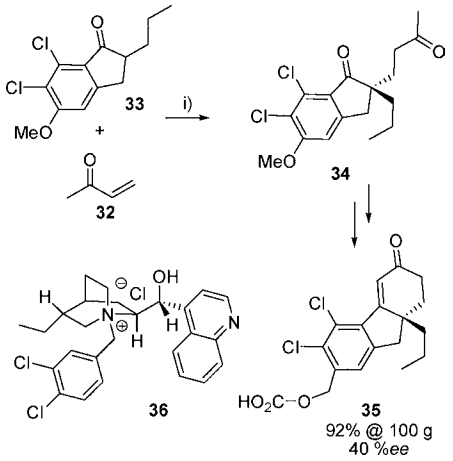
2.3. Michael Addition (ACA) Using Phase Transfer Catalysis. Phase transfer catalysis (PTC) has proven particularly viable for large- and industrial-scale applications over the last few decades, mainly due to the mild reaction conditions that are typically employed. Examples of multikilo, operationally simple PTC processes that employ simple, environmentally benign solvents and relatively cheap catalysts can be found in reasonable abundance.[13] The desirable traits of PTC are accompanied by some inherent scale-up issues, however; the use of biphasic systems necessarily requires close scrutiny of mixing effects (which can greatly affect reaction kinetics and selectivity) and separation/disposal of two or more immiscible waste streams.

As early as the mid 1980s, scientists from Merck demonstrated that cinchona derivatives such as **36** (Scheme 10) could catalyse the Michael addition of ketone **33** with methyl vinyl ketone (**32**, MVK) under mild conditions and, crucially, at large scale.[14] The ultimate goal of this study programme was the synthesis of drug candidate **35** (and analogues) for the treatment of brain edema and traumatic head injury.[15]

This reaction was carried out under various conditions, and the operationally simple liquid/solid system shown in Scheme 10 gave excellent isolated yield at 100-g scale albeit with modest levels of enantioselectivity. This early example showed the potential power of the asymmetric PTC reaction for industrial-orientated synthesis; enantioselective synthesis of a quarternary stereocentre under mild and benign conditions remains an impressive achievement.

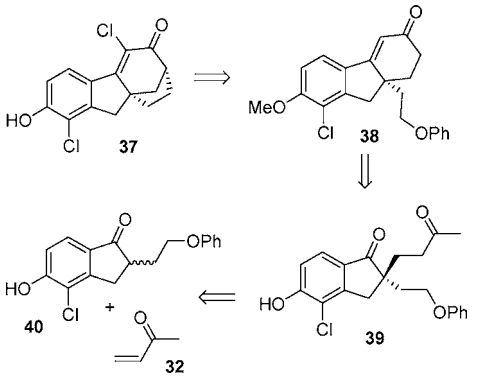
The learning generated in the previous example was (presumably) of great benefit to the scientists at Merck when further developing the Michael addition/Robinson annulation approach to the structurally similar target **37** (Scheme 11).[16] As

Scheme 10. Early examples of asymmetric PTC[a]



[a]Reagents and conditions: i) **33** (1.0 equiv), **32** (1.0 equiv), **36** (5.5 mol %), KOH (2.0 equiv), toluene (25 vol), RT, 1.5 h.

Scheme 11. Michael addition/Robinson annulation at kilogram scale



part of a research programme aimed at finding selective modulators of estrogen receptor-β for the treatment of menopausal symptoms, a multikilogram synthesis of **37** was designed and developed.

For the key transformation (**40** → **39**, Table 2), a significant amount of effort was directed towards the understanding and optimisation of key reaction parameters. After optimisation of catalyst structure (*N*-substituents and counterion), quarternary salt **43** was selected for further scale-up on the basis of the achieved enantioselectivity (50−54% ee) and commercial availability of the catalyst components.

As mentioned earlier, PTC chemistry of this sort is intrinsically sensitive to mixing and solution parameters, and this was clearly exemplified in these studies. It was found that a catalyst concentration of >8 mg/mL (organic phase) was necessary to obtain acceptable levels of enantioselectivity (>50 % ee), and this could only be achieved by slurry treatment of **41** and **43** in toluene and sodium hydroxide for an extended period *prior* to exposure to methylvinyl ketone **32**. Moreover, catalyst **41** that had been prepared in THF displayed a larger mean particle size (~65 μm) than that prepared in toluene (~44 μm); this resulted in *decreased* solubility in the organic phase, poorer extraction, and diminished levels of stereoselectivity. Another common observation for this type of PTC reaction was made; efficient mixing was *critical* in extracting the catalyst into the organic phase during the Michael reaction. The high

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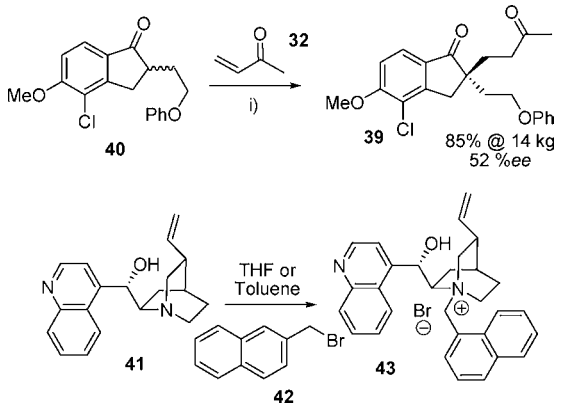
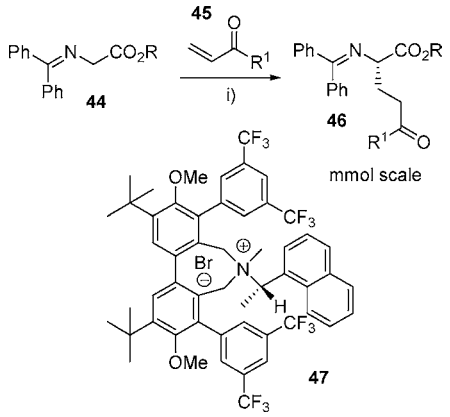
Table 2. Solvent effects on catalyst performance[a]



entry	time (min)	catalyst conc[b] (mg/mL)	catalyst conc[c] (mg/mL)
1	120	2.0	2.6
2	240	3.3	6.1
3	390	4.3	9.6
4	4080	14.6[d]	13.9[d]

[a]Conditions and reagents: i) **43** (15 mol %), **40** (1.0 equiv), toluene (20 vol), NaOH (50% aq, 15 vol), RT, 14 h then **32** (1.0 equiv) in toluene (2.5 vol). [b]Phase transfer catalysts prepared in THF where particle size 95% < 65 μm. [c]Phase transfer catalysts prepared in toluene where particle size 95% < 44 μm. [d]Theoretical maximum catalyst concentration of 14.0 mg/mL based on charge.

Table 3. Potentially scaleable examples of PTC[a]



entry	R	R^1	time (h)	yield (%)	% ee[b]
1	Ph_2CH	Me	2	84	94
2	^{t}Bu	Me	2	94	91
3	Ph_2CH	Me	18	45	60
4	Ph_2CH	Et	18	74	92
5	Ph_2CH	$^n C_5H_{12}$	18	60	94
6	Ph_2CH	O^{t}Bu	18	<10	–
7	Ph_2CH	NMe_2	18	<10	–

[a]Reagents and conditions: i) **47** (1 mol %), **44** (1.0 equiv), **45** (2.0 equiv), Cs_2CO_3 (50 mol %) $^i Pr_2O$ (typically 0.3 M), 0 °C. [b]Determined via HPLC analysis of crude product.

density (1.52 g/mL) of 50% NaOH (aq) meant that overhead-stirring with screw propellers at >500 rpm (tip speed 1.8 m/s) was essential to obtain satisfactory results in the laboratory; at pilot-plant scale (400 L), agitation rates of 220 rpm (tip speed 5 m/s) were more than adequate. Other observations included the requirement to avoid the ingress of oxygen into the system (via nitrogen sparging at large scale) which was found to lead to oxidation byproduct.

The above two examples show that even after considerable effort and cost directed toward process development it can be extremely challenging to find high-performance systems that satisfy the necessary criteria for scale-up.

Moving away from the Michael/Robinson approaches discussed above, examples of other potentially scaleable, Michael additions have been reported using PTC. As in the prior examples, quaternary ammonium ions are typically used as catalysts in solid/liquid systems. In 2005, Lygo et al. published a brief study on the scope and optimisation of the asymmetric Michael addition of glycine imines to α,β-unsaturated systems (Table 3).[17] As might be expected for these biphasic reactions, the observed yields and enantiose-

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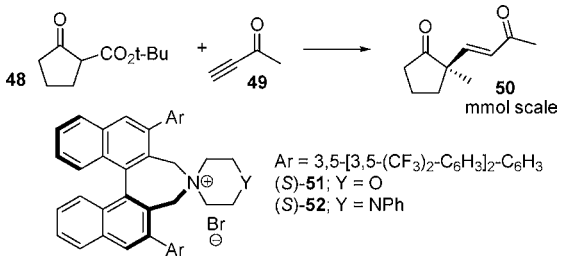
Table 4. PTC addition of β-ketoesters



entry	catalyst	solvent	conditions[a]	yield[b] (%,E/Z)[c]	% ee[d] (E/Z)
1	(S)-**51**	toluene	0 °C, 2 h	75/24	69/51
2	(S)-**51**	*m*-xylene	0 °C, 1 h	72/27	76/57
3	(S)-**51**	*o*-xylene	0 °C, 1 h	73/21	72/57
4	(S)-**51**	CF_3-Ph	0 °C, 1 h	70/29	55/33
5	(S)-**51**	THF	0 °C, 1 h	59/40	25/17
6	(S)-**51**	MTBE	0 °C, 1 h	68/31	77/67
7	(S)-**51**	CPME	0 °C, 1 h	66/33	76/65
8	(S)-**51**	Et_2O	0 °C, 1 h	58/39	81/75
9	(S)-**51**	Et_2O	−40 °C, 2.5 h	62/37	87/79
10	(S)-**52**	Et_2O	−40 °C, 3 h	54/45	90/85
11	(S)-**52**	Et_2O	−40 °C, 8 h	54/45	91/84

[a]Reagents and conditions: 1.5 equiv 3-butyne-2-one (**49**), 1 mol % catalyst, and 0.5 equiv K_2CO_3 used, unless stated otherwise. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by HPLC.

lectivities were found to be very sensitive to base and solvent selection.

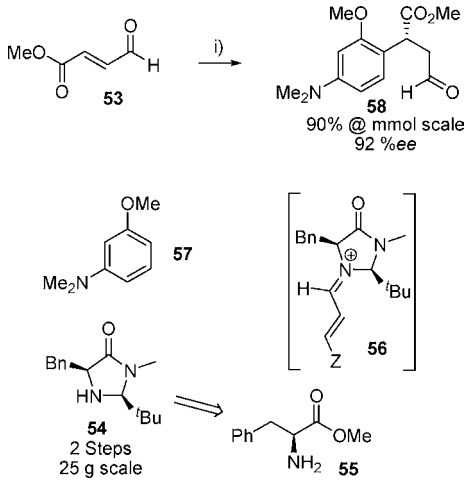
Using a low loading of catalyst **47**, a range of protected glycine imines were coupled with α,β-unsaturated ketones **45** using cesium carbonate in diisopropyl ether at 0 °C. This protocol represents a simple route to substituted amino acids which are crucial building blocks for a range of industrial applications. It is likely that this methodology would also be subject to the subtleties discussed previously (solution and mixing effects, particularly when using high-density solids such as Cs_2CO_3) and the safety aspects of diisopropyl ether[18] would likely lead to scale-up issues, but regardless, the potential for larger-scale application is obvious due to the straightforward, mild reaction conditions.

Similar reports by Maruoka et al. describe Michael addition of β-keto-esters **48** to acetylinic ketones **49** under equally mild and scaleable conditions (Table 4).[19] As with the other PTC examples already mentioned, the sensitivity to solvent was pronounced.

Interestingly, the conditions outlined in entry 11 were deemed optimal and subjected to further study. It could be argued that, in the event of scale-up for further study, entries 1−3 would be more suitable since they contain a higher absolute amount of the major stereoisomer [i.e., (*S*,*E*)-**50**]; also, the conditions employed in entry 11 are less favorable based on temperature (−40 °C vs 0 °C) and solvent selection (diethyl ether vs toluene, which requires specialist plant facilities).

2.4. Michael Addition (ACA) Using Organocatalysis. The rapid proliferation of literature concerning organocatalysis since the year 2000 has been discussed in-depth in a range of high-quality review papers.[20] The potential power and utility of this area of organic chemistry was apparent very early on in the development of the topic, and there have been an impressive number of new methodologies developed that either have, or potentially could be, utilised at larger scales. This branch of chemistry holds particular interest for process chemists since it allows for asymmetric synthesis without the need for metals and the associated problems (toxicity, air-sensitivity, etc.). The realisation that organocatalysis was particularly applicable to Michael addition chemistry resulted in much of the early intellectual property being protected. The MacMillan group filed a series of patents in 2002−2003 describing enantioselective 1,4-addition of various aromatic nucleophiles to α,β-unsaturated carbonyl compounds (Scheme 12).[21] In the example shown, Michael acceptor **53** is activated via (LUMO-lowering) iminium ion formation with **54** towards nucleophilic attack by **57**. Although only demonstrated on small scale, the power of this particular methodology lies in the readily obtainable catalyst **54**, and the operational simplicity of the process.

Scheme 12. LUMO-lowering activation via organocatalysis[a]



[a]Reagents and conditions: i) **53** (1.0 equiv), **57** (1.2 equiv), **54** (10 mol %), CH_3Cl (1 vol), HCl (10 mol %, 4 M in dioxane), −20 °C, 8 h.

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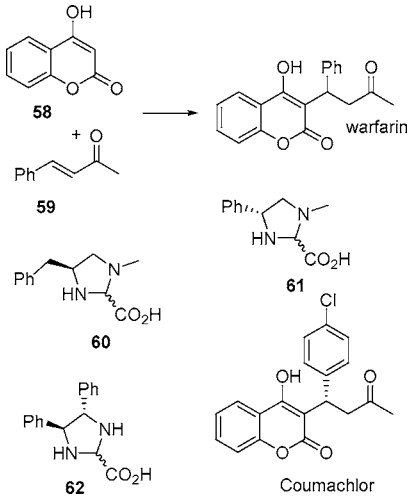
Table 5. Organocatalytic synthesis of warfarin[a]



entry	catalyst	[mol %]	solvent	time	yield (%)[b]	% ee[c]
1	(*S*)-proline	50	DMSO	15	85	0
2	**60**	10	DCM	70	77	62 (*S*)
3	**60**	5	THF	70	85	70 (*S*)
4	**60**	10	EtOH	70	69	47 (*S*)
5	**60**	10	H_2O	90	22	49 (*S*)
6	**61**	10	THF	130	83	56 (*S*)
7	(*R*,*R*)-**62**	10	DCM	150	96	82 (*S*)[d]
8	(*S*,*S*)-**62**	10	THF	130	90	80 (*S*)[d]

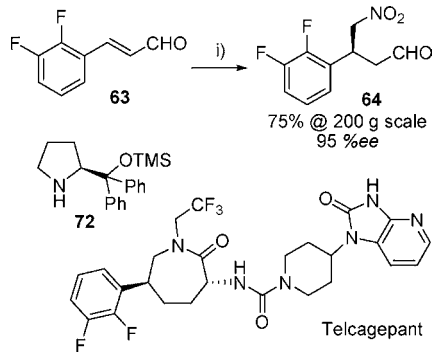
[a]Conditions and reagents: **58** (1.0 equiv), **59** (1.05 equiv) and catalyst was stirred at ambient temperature for the indicated time. The crude mixture was then purified by flash column chromatography. [b]Yield after purification. [c]Determined by HPLC. [d]Enantiomeric purity increased to 99.9 % ee by recrystallisation from water/acetone.

Although the majority of the organocatalytic Michael addition methodologies (as exemplified above) have not been demonstrated on any significant scale, the ability to *β*-functionalise carbonyl compounds asymmetrically, without using potentially toxic or expensive transition metal catalysts, remains a desirable goal for industrial applications. In terms of large-scale examples, the synthesis of warfarin (Coumadin; the world's most prescribed anticoagulant)[22] has been demonstrated. Publications from 2003 by Jørgensen et al.,[23] document very short and expedient routes to warfarin and its analogues using simple, organocatalysed Michael-addition reactions (Table 5). The approach is the same as the commercial synthesis of Coumadin in a retrosynthetic sense, involving conjugate addition of 4-hydroxycoumarin **58** to benzylideneacetone **59**, but crucially, the presence of imidazolidine catalyst **62** affords an *enantioselective* reaction whilst the commercial synthesis is *racemic*. The origin of the enantioselectivity is postulated as an iminium species analogous to that depicted above (**56**, Scheme 12).

As seen in the data above, this reaction represents an exceptionally expedient route to a commercial drug product and has also been demonstrated at kilo scale with recycled catalysts without loss of yield or selectivity. Although the reaction times are somewhat lengthy, the simple and benign conditions (entries 3 and 8 in particular) would make this an attractive alternative to the current syntheses. This report also demonstrates the synthesis of warfarin analogues such as Coumachlor, a potent rodenticide.

The calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant (Scheme 13) has recently proven effective for the treatment of migraine in phase III clinical trials.[24] This structure, which has been synthesised using Hayashi–Miyaura coupling (see section 3.4) can also be accessed using organocatalytic ACA. The combination of aldehyde **63**, nitromethane, and modified prolinol catalyst **72** afforded the desired adduct **64** with good yield and excellent enantioselectivity. A unique, yet effective "cocktail" of cocatalysts (pivalic/boric acid) and solvents (THF/water) was required to maintain a balance between reactivity and product stability; careful attention was also given to the formation of various associated impurities.

Scheme 13. Organocatalytic synthesis of telcagepant[a]



[a]Reagents and conditions: i) **63** (1.0 equiv), pivalic acid (5 mol %), boric acid (0.5 equiv), **72** (5 mol %), nitromethane (6.0 equiv), THF (14 vol), water (2 vol), RT, 30 h.

Iminium ion organocatalysis has been utilised in the synthesis of other pharmaceutical agents. A number of brief (formal) syntheses of paroxetine (originally marketed by GlaxoSmithK-

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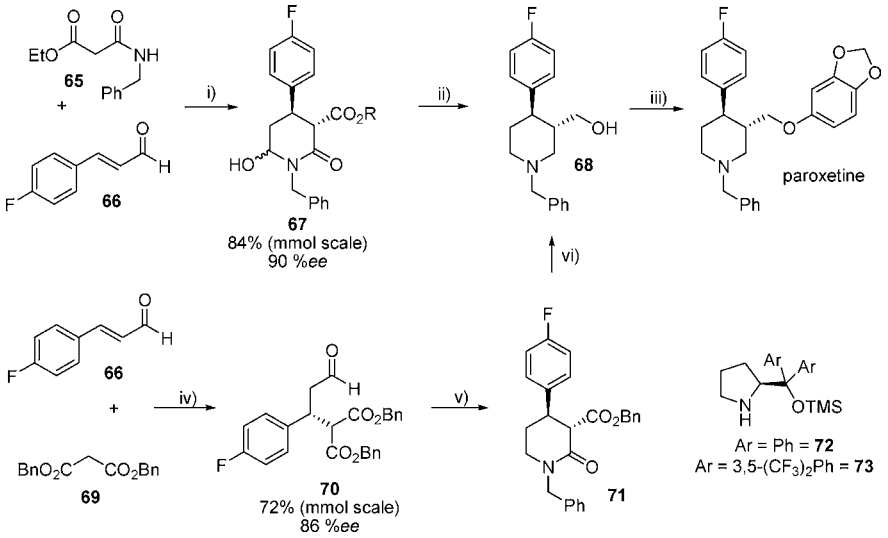
Scheme 14. Formal synthesis of (−)-paroxetine[a]



[a]Reagents and conditions: i) **65** (1.2 equiv), **66** (1.0 equiv), **72** (20 mol %), KOAc (1.2 equiv), CF_3CH_2OH (0.3 M), RT, 16 h; ii) BH_3, THF, RT, 76%; iii) reference 27; iv) **66** (2.0 equiv), **69** (1.0 equiv), **73** (10 mol %), EtOH (0.5 M), 0 °C, 96 h; v) $PhCH_2NH_2$, $NaBH(OAc)_3$, dioxane, 70%; vi) $LiAlH_4$, THF, reflux, 85%.

line as Seroxat, a blockbuster selective serotonin reuptake inhibitor [SSRI] for the treatment of depression and anxiety-related disorders) have been described. Using simple building blocks (Scheme 14; fluoro-cinnamaldehyde **66** and malonate derivative **65**) with a silylated prolinol **72** as catalyst, Michael addition was shown to proceed in good yield and stereoselectivity.[25] A previous example had also shown potentially scaleable Michael addition (Scheme 14; **66** + **69** → **70**).[26]

In both cases, the nature of the solvent was highlighted as a key parameter, and polar-aprotics were required. Whilst the latter example (**66** + **69** → **70**) utilised a much more industrially friendly solvent (ethanol vs trifluoroethanol), the required reaction times were greater, running into multiple days. Regardless, the potential step-saving in these routes (current industrial syntheses are typically 10−15 steps) is significant, and the simplicity of the chemistry involved makes for suitable candidates for further scale-up activities.

3. ADDITION OF NONSTABILISED ORGANOMETALLIC NUCLEOPHILES

In the previous section, classical Michael additions were considered where "soft" or stabilised C−H nucleophiles were added to conjugated systems in order to form new C−C bonds asymmetrically. An alternative approach is to use "hard" or nonstabilised organometallic nucleophiles generated from simple, nontransition metals such as zinc, magnesium (Grignard), boron, aluminium, and lithium species.[28] These reagents tend to be significantly more reactive than the enolate-types discussed previously, and in the absence of a suitable additive or catalyst, selectivity for the desired 1,4-addition vs competing 1,2-addition is seldom seen. The most common mode of stereochemical induction is via the addition of transition metal/ligand complexes (catalytic or stoichiometric), and in order to achieve this, copper[29] and rhodium[30] are by far the most studied.

In terms of the organometallics used, the challenges associated with controllable reactivity and safe-handling mirror the general trend in reactivity: RLi > R_3Al > RMgX > R_2Zn > RBX_2 (aryl boronic acids). In very loose terms, this means that, when considering controllable and scaleable conjugate addition, examples become more abundant as we move along the series from RLi → RBX_2.

3.1. Organo Lithium and -Aluminium Reagents for ACA and DCA. Although organolithium nucleophiles (mainly "soft" enolate-types) have been widely used for industrial asymmetric synthesis,[31] the challenges associated with alkyl- or aryllithium reagents are such that examples of *scaleable* asymmetric conjugate addition (ACA) could not be found for this review. Diastereoselective conjugate addition (DCA) using chiral, nonracemic substrates with organolithium species have been reported at significant scales, however. Transmetalation of highly reactive organolithium species to "softer", more selective (toward 1,4-addition) organocuprates is a common method for DCA. As reported by Japan Tobacco Incorporated in 1991, alkylation of levoglucosenone **74** (Scheme 15) with methyllithium and copper(I) iodide proceeded smoothly as part of a synthetic route to "whisky lactone" (and other *trans*-lactones found in fragrances and pheromones).[32] The same approach has been employed in the synthesis of steroid analogues[33] as well as pharmaceuticals such as Travoprost.[34] An interesting series of papers by scientists at Merck and Banyu described DCA with aryllithium **77**.[35] Interestingly, this procedure (which is a variation of a method described by Alexakis)[36] did not require the addition of copper(I) salts; good selectivity for 1,4-addition product **78** was achieved en route to endothelin A receptor (ETA) antagonists.

As with organolithium compounds, large-scale examples of ACA with organoaluminium compounds could not be found for this review. In the last 5 years, however, literature examples of ACA using trimethylaluminium ($AlMe_3$) have been reported, some of which show potential for larger-scale application. The examples shown in Table 6 take advantage of the high-reactivity of organoaluminium reagents to enable conjugate addition to β-disubstituted cyclic enones **79**; this is noteworthy since these hindered electrophiles rarely undergo ACA, and the resulting products **80** contain newly formed, quarternary stereocentres.

The two methods described (above) by Alexakis[37] and Hoveyda[38] use complementary approaches to synthesise similar

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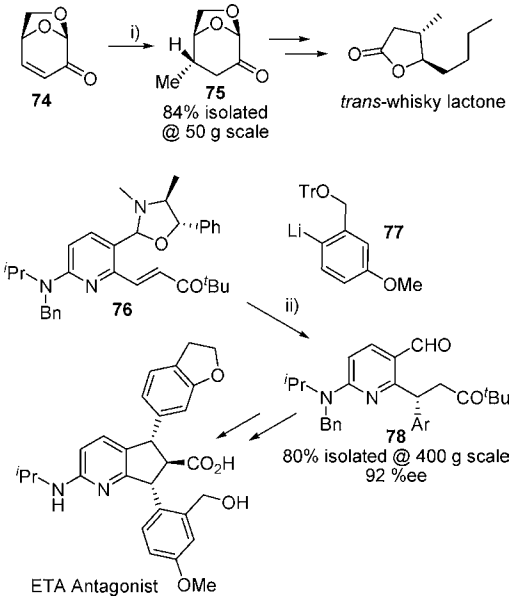
Scheme 15. DCA with organolithium reagents[a]



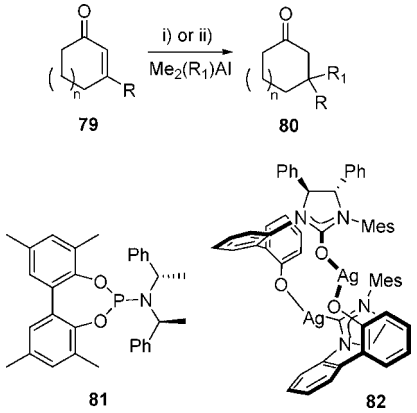
[a]Reagents and conditions: i) CuI (1.0 equiv), MeLi (1.4 M in Et_2O, 2.0 equiv), **74** (1.0 equiv) in Et_2O (1.1 vol), −60 to −20 °C, 30 min.; ii) **77** (1.0 equiv), THF (5 vol), toluene (5.0 vol), ^{n}BuLi (1.6 M, 1.50 equiv), −70 °C, 20 min then **76** (1.0 equiv) in toluene (5 vol), −60 °C, 25 min.

structural motifs; the former approach utilises addition of simple trimethylaluminium to more complex cyclic enones; the latter approach utilises addition of more complex dimethylarylaluminium reagents to simpler cyclic enones. Although both protocols have only been demonstrated on milligram scale, the experimental conditions described could be amenable to further scale-up activities.

3.2. Grignard Reagents for Asymmetric Conjugate Addition (ACA). Organozinc reagents have undoubtedly attracted the most attention for ACA in the academic community,[29a−c] but Grignard reagents are probably more amenable for large-scale applications based on (i) availability (there are more commercially available Grignard reagents than organozincs); (ii) efficiency (half of the functionality in R_2Zn is typically wasted); (iii) economy (simple dialkylzinc solutions are typically 5−10 times more expensive than the corresponding Grignard),[39] and (iv) toxicity (zinc has a *permitted* daily exposure (PDE) of around 15 mg/day for adult males vs a *recommended* daily allowance (RDA) of 400−500 mg/day for magnesium).[10] From a process safety perspective, although both types of reagent are potentially hazardous, Grignard species may be preferred due to lower flammability.

Although initially described in 1988,[40] it was not until 2004 that ACA with simple Grignard reagents could be achieved with high levels of enantioselectivity.[41] Subsequently, a number of procedures have been generated that allow for ACA of simple Grignard reagents. As shown in Scheme 16, highly selective ACA with MeMgBr has been utilised with α,β-unsaturated esters (**83**)[42] and thioesters (**85**)[43] to achieve iterative syntheses of extended polypropionate units such as those found in the antibiotic TMC-151A and phthioceranic acid (a heptamethyl-branched fatty acid isolated from the cell wall of

Table 6. Copper-mediated ACA with organoaluminium reagents[a]



entry	n	R	R_1	catalyst	conditions	yield (%)	% ee[b]
1[c]	1	Et	Me	CuTC (2 mol %), **81** (4 mol %)	Et_2O, −30 °C, 18 h	78	94
2[c]	1	^{i}Bu	Me	CuTC (2 mol %), **81** (4 mol %)	Et_2O, −30 °C, 18 h	35[d]	93
3[c]	1	$(CH_2)_2CHCH_2$	Me	CuTC (2 mol %), **81** (4 mol %)	Et_2O, −30 °C, 18 h	95[d]	91
4[c]	1	$(CH_2)_3CHCH_2$	Me	CuTC (2 mol %), **81** (4 mol %)	Et_2O, −30 °C, 18 h	95[d]	93
5[e]	0	Me	Ph	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −50 °C, 48 h	66	72
6[e]	0	Me	*o*-MeC_6H_4	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −15 °C, 48 h	85	98
7[e]	0	Me	*p*-$OMeC_6H_4$	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −50 °C, 48 h	67	71
8[e]	0	Me	*o*-$OMeC_6H_4$	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −15 °C, 48 h	55	95
9[e]	1	Me	Ph	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −30 °C, 36 h	71	90
10[e]	1	Me	*o*-MeC_6H_4	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, +4 °C, 42 h	49	96
11[e]	1	Me	*p*-$OMeC_6H_4$	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −50 °C, 36 h	61	84
12[e]	1	Me	*p*-$CF_3C_6H_4$	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, −30 °C, 36 h	52	86
13[e]	1	Me	*o*-$OMeC_6H_4$	$Cu(OTf)_2$ (5 mol %), **82** (2.5 mol %)	THF, +4 °C, 48 h	60	83

[a]Reagents and conditions: i) CuTC/**81** or ii) $Cu(OTf)_2$/**82**. [b]Determined by HPLC/GC. [c]Reference 37. [d]Conversion (not isolated). [e]Reference 38.

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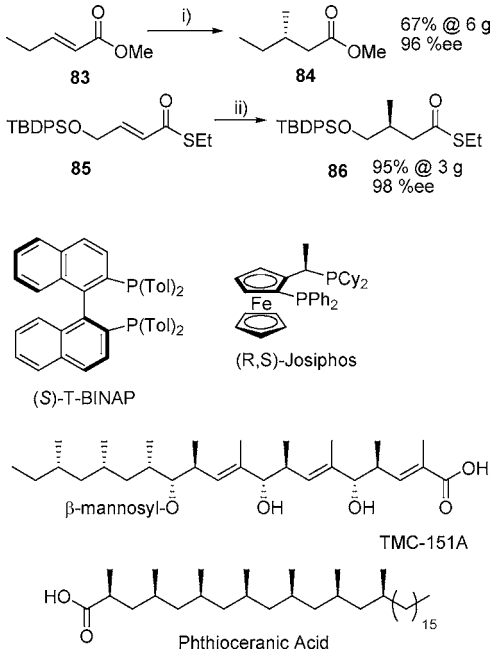
Scheme 16. ACA with MeMgBr for deoxypropionate synthesis[a]



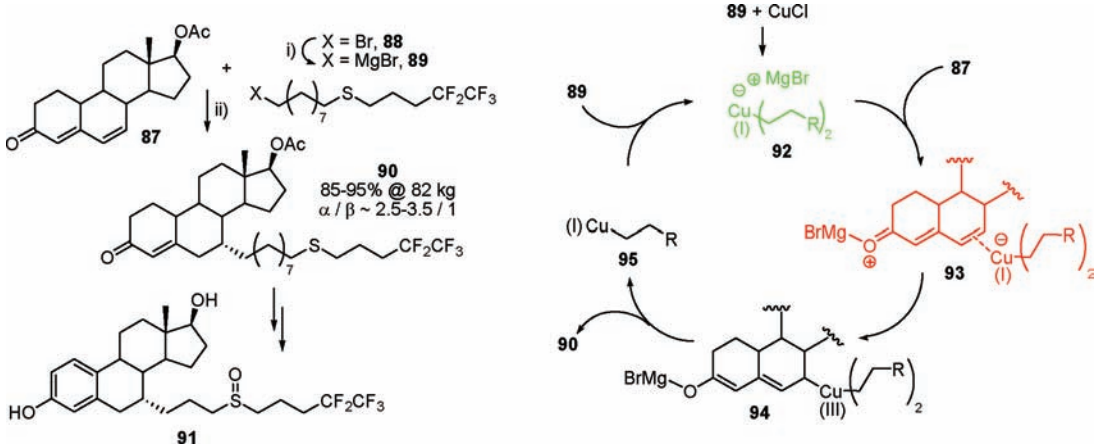
[a]Reagents and conditions: i) (*S*)-T-BINAP (3 mol %), CuI (2 mol %), MTBE (35 vol), −20 °C, 20 min, then MeMgBr (3.0 M in Et_2O, 5.1 equiv), and then **83** (1.0 equiv) in MTBE (10 vol), −20 °C, 1 h; ii) **85** (1.0 equiv), MeMgBr (1.2 equiv), CuBr (1 mol %), (*R*,*S*)-Josiphos (1 mol %), MTBE (15 vol), −78 °C, 18 h.

Mycobacterium tuberculosis). Both of the procedures shown utilise commercially available copper-based catalysts and standard solutions of methylmagnesium bromide. An industrially amenable solvent (MTBE) is also used, and in the case of the first example (**83** → **84**), plant-accessible temperatures are used. These reactions have currently only been demonstrated on gram scale, but there is potential for further scale-up.

Again, as with the organolithium and -aluminium ACA procedures, the author has been unable to find any examples which demonstrate the use of Grignard reagents at 100-gram scale or greater. There are large-scale examples of *diastereoselective* conjugate addition (DCA) using Grignard reagents, however, and inspection of these gives an insight into the associated subtleties and nuances that perhaps explain why large-scale ACA processes are absent thus far. In a series of publications, process scientists at AstraZeneca describe large-scale copper-catalysed DCA as a route to synthesising the established breast cancer drug fulvestrant (Faslodex; Scheme 17).[44]

Development of this protocol uncovered a number of critical parameters that required close attention. First, dialkylcuprate **92** had to be preformed below −20 °C; higher temperatures led to degradation. If **92** was not preformed and the process was run 'all-in' (i.e., **87** + **89** + CuI → **90**), almost exclusively 1,2-addition was observed (**87** + **89**). Close scrutiny of the process and its putative mechanism (Scheme 17) led to the hypothesis that, under low catalytic loadings of copper, the formation of σ-Cu(III) species **94** and subsequent reductive elimination to the Cu(I) species **95** was being out-competed by enolate formation (deprotonation of **87** with excess **89**) and 1,2-addition (**87** + **89**). It was found that careful, *portionwise* addition of dienone **87** to cuprate **92** with *colorimetric* monitoring allowed for successful optimisation of the various processes involved. If addition of dienone **87** was too fast (portions too large or added too rapidly), persistent red/orange colouration was noted (attributed to π-complex **93**) indicating enone saturation which quickly led to enolisation and 1,2-addition. Optimum addition rates of dienone **87** to cuprate **92** were indicated by steady oscillations between red/orange (π-complex **93**) and yellow/green colouration (cuprate **92**). Consideration of the safety aspects of large-scale Grignard generation was also necessary, and this is an aspect that is often overlooked on smaller, laboratory scales. In the above example, the calculated heat output for the transformation **88** → **89** was high (270 kJ mol^{-1}) and would result in an unacceptable adiabatic temperature rise (~65 °C). This required portionwise addition of alkyl bromide **88** to a suspension of magnesium raspings in THF (containing a small portion of **89** from a previous batch as initiator) at 45 °C. Alternative processes for Grignard formation at large scale have recently been reported[45] and are likely to make ACA (or DCA) with Grignard reagents a more attractive option.

Scheme 17. Synthesis of fulvestrant via DCA[a]



[a]Reagents and conditions: i) **88** (0.20 equiv), magnesium rasping (1.15 equiv), I_2 (0.1 mol %), THF (4.75 vol), 45 °C; then further **88** (0.80 equiv); ii) **89** (1.35 equiv), THF (2.1 vol), −34 °C; then CuCl (7.8 mol %); then **87** (1.0 equiv) in THF (4.7 vol) over 3.5 h, −34 °C.

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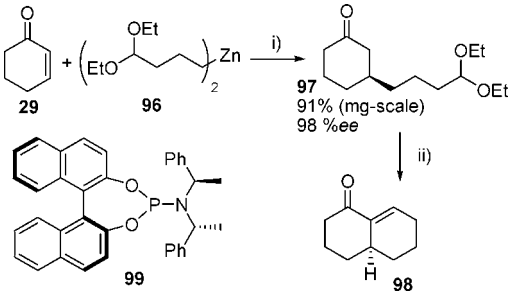
3.3. Organozinc Reagents for Asymmetric Conjugate Addition (ACA). Organozinc reagents have seen the most widespread application in the academic community for achieving asymmetric conjugate addition (ACA). Organozincs are typically viewed as the most useful from an academic sense due to their tempered reactivity;[46] this allows for both better functional group tolerance and control of racemic background reactivity when utilising asymmetric catalysis. Examples of *potentially* scaleable procedures have been known for over a decade; in 1999 Feringa et al. described an expedient and selective synthesis of bicyclic enone **98** under industrially amenable conditions with a (now) commercially available ligand **99** (Scheme 18).[47] This procedure, whereby dialkylzinc

Scheme 18. ACA with dialkylzinc reagents[a]

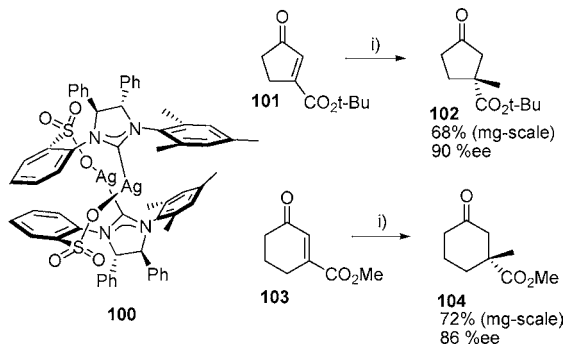


[a]Reagents and conditions: i) $Cu(OTf)_2$ (2 mol %), **99** (4 mol %), toluene (~0.1 M), RT, 1 h. then **29** (1.0 equiv), **96** (1.9 equiv), −30 °C to RT, 16 h.

species **96** is converted to a chiral cuprate nucleophile, allows for impressive levels of stereocontrol.

The overwhelming majority of methodologies for ACA with organozincs are developed for diethylzinc addition. Unfortunately, at least from a *pharmaceutical* viewpoint, there are scant molecules of interest bearing ethyl-substituted stereocentres. The inclusion of *methyl*-substituted stereocentres is of far greater importance, and there are now a handful of protocols for achieving dimethylzinc addition under mild and scaleable conditions. Using chiral N-heterocyclic carbene (NHC) copper complex **100**, dimethylzinc can be added to *β*-substituted alkenones **101** and **103**, thus generating quarternary stereogenic centres bearing a synthetically useful ester functionality (Scheme 19).[48] Although these reactions have only been carried out on milligram scale thus far, care has been taken to

Scheme 19. ACA with NHC–Cu Complexes[a]



[a]Reagents and conditions: i) **101** or **103** (1.0 equiv), **100** (2.5 mol %), $(CuOTf)_2 \cdot C_6H_6$, Me_2Zn (3.0 equiv), MTBE (0.1 M), −30 °C, 15–42 h.

use commercial, unpurified reagents and solvents under "bench-top" conditions; there is definite scope for further scale-up of these conditions.

Despite these impressive and seemingly scaleable examples, no large-scale examples of ACA using organozinc reagents could be found.

3.4. Organoboron Reagents for Asymmetric Conjugate Addition (ACA). Asymmetric conjugate addition using organoboron nucleophiles is another area that has been extensively studied over the last 10–15 years. Originally described by Hayashi and Miyaura in 1997–1998,[49] conjugate addition of arylboronic acids using rhodium catalysis has become a versatile tool for asymmetric synthesis. Arylboronic acids are widely employed in industrial chemistry due to availability, low reactivity, and ease of handling; these are strong contributing factors in the proliferation of such methodologies. A second-generation route to telcagepant (Table 7), a calcitonin gene-related peptide (CGRP) receptor antagonist for the treatment of migraine, was developed at Merck utilising Hayashi–Miyaura coupling.[50] The remote stereocentre in nitroolefin **105** did not promote diastereoselectivity in the 1,4-addition reaction when achiral (or racemic, entry 3) ligands were used. Commercially available chiral ligand ([*S*]-BINAP) was employed to yield the desired (6*S*)-isomer of **107**. Careful attention to suppress degradation of arylboronic acid **106** was successful, although 2.5 equiv of **106** was still required; this is a continuing theme with much chemistry using arylboronic acids. Regardless, isolated yields and observed selectivity were impressive at 2-kg scale.

Availability and reliability of transition metal catalysts can be a problem for scale-up studies, and this certainly applied in early iterations of Hayashi–Miyaura coupling. As the research area has matured, however, industrially applicable examples have appeared where effort has been directed towards the development of stable and easily handled catalyst systems. After disappointing results following literature procedures, scientists at Abbot described a simple method for the in situ formation of "Miyaura catalyst" **108** (Table 8). It was noted that the rhodium–norbornadiene (NBD) precursor gave intrinsically slower (racemic) background reactivity than the more typical cyclooctadiene (COD) analogue. In this way, highly stereoselective and, more importantly, *repeatable* ACA was demonstrated with a range of substrates at 10-g scale (cinnamaldehyde (entry 3) being the only exception). Moreover, careful optimisation of conditions allowed the arylboronic acid reagents to be employed in nearly equimolar amounts (w.r.t. **109**) without significant losses to competing protodeboronation or hydrolysis.

The procedure outlined above was subsequently scaled-up to 100 g in order to access both enantiomers of **112b** (Scheme 20) and subsequently all four stereoisomers of VPC01091, an S1P1 receptor agonist for the treatment of relapsing remitting multiple sclerosis (RRMS).[51]

In 2008, process scientists at AstraZeneca reported a highly developed example of transition-metal-mediated ACA using organoboron reagents (Hayashi–Miyaura coupling).[52] To the best of the author's knowledge, this is the largest example (at 20 kg) of asymmetric C–C bond formation using transition-metal-catalysed conjugate addition of organometallic reagents (Scheme 21).

This report gives an indication of the rigour and attention to detail that is required to convert an academic scale reaction into a viable multikilogram process. In its most simple guise, the

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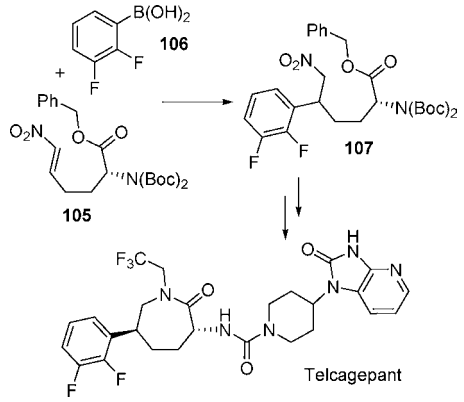
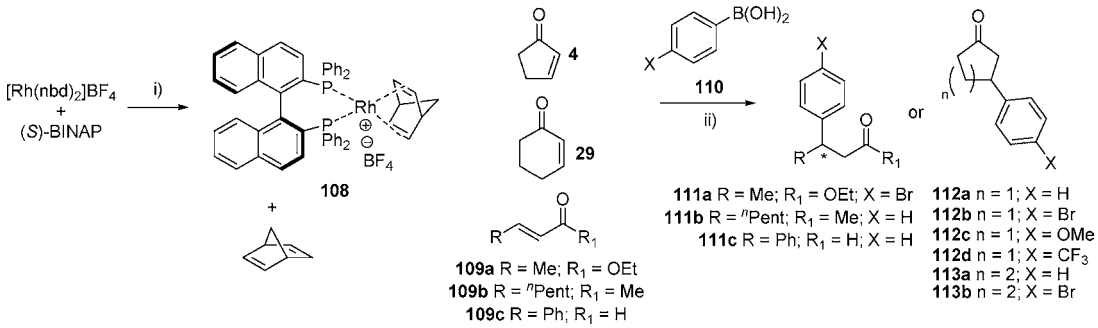
Table 7. Hayashi–Miyaura coupling for the synthesis of telcagepant[a]



entry	BINAP	T °C	mol % cat.	yield (%)	6*S*:6*R*
1	*S*	45	10–20	80	93:7[b]
2[c]	*S*	35	2.5	96 @ 2 kg	93:7[d]
3[c]	*rac*	35	3	50[e]	41:59[d]
4[c]	*R*	35	3	76[e]	3:97[d]

[a]Reagents and conditions: i) **105** (1.0 equiv), **106** (2.5 equiv), $Rh(acac)(C_2H_4)_2$/BINAP, dioxane, H_2O, 12 h. [b]Ratio determined by NMR. [c]50 mol % $NaHCO_3$ was added. [d]Ratio determined by HPLC. [e]Nonoptimised conditions.

Table 8. ACA with rhodium catalysis[a]



entry	product	yield (%)[b]	purified yield (%)[c]	% ee
1	**111a**	99	79	93
2	**111b**	92	72	92
3	**111c**	–	n/a	n/a
4	**112a**	90	78	95
5	**112b**	96	85	97
6	**112c**	93	75	96
7	**112d**	96	81	97
8	**113a**	94	80	99
9	**113b**	86	71	99

[a]Reagents and conditions: i) $[Rh(nbd)_2]BF_4$ (1.5 mol %), (*S*)-BINAP (1.7 mol %), **110** (1.05 equiv), dioxane (6.5 vol), RT, 2 h then water (1 vol), TEA (1 equiv), **4**/**29**/**109** (1.0 equiv), RT, 15 h. [b]Solution yield determined by HPLC. [c]Isolated yield postchromatographic purification.

reaction depicted in Scheme 21 was successfully demonstrated relatively quickly, but a much greater package of work was required to develop a process that satisfied each of the SELECT criteria[2] introduced at the start of this review.

Considering the **S**afety aspects of SELECT,[2] typical residual rhodium levels in **115** (~200 ppm) represented toxicological risks (rhodium has a permitted daily exposure (PDE) of 2.6 μg/kg/day).[10] Efficient removal of rhodium required careful oxidation of the catalyst postreaction (Oxone) and subsequent scavenging (Smopex 234). In this way, rhodium levels of below 30 ppm could be achieved at up to 20-kg scale. Arylboronic ester **114a** (then £5600 per kilogram) made the process nonviable (**E**conomy); modifications allowed the use of the parent boronic acid **114b** (then £750 per kilogram). The initial solvent system (THF/water) led to unacceptable levels of protodeboronation (conversion of **114b** to difluorobenzene), impacting on **E**conomy and **T**hroughput; exchange of water for IPA greatly alleviated this problem (~8% degradation with ^{i}PrOH vs 30% with water in comparable timeframes as determined by ^{19}F NMR). The O^{i}Pr ester **113** was carefully chosen to give an acceptable balance between stereoselectivity (**C**ontrol; bulkier esters → more selectivity) and reactivity (**T**hroughput; bulkier esters → long reaction times). The combination of K_3PO_4 and THF/water resulted in agglomeration of large lumps of material inside the reaction vessel. Replacement with K_2CO_3 (325 mesh) and THF/IPA gave a

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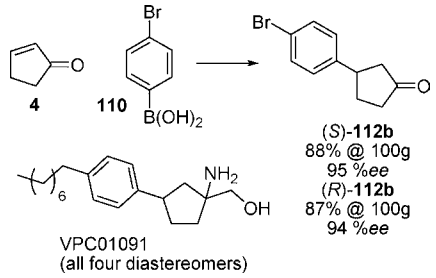
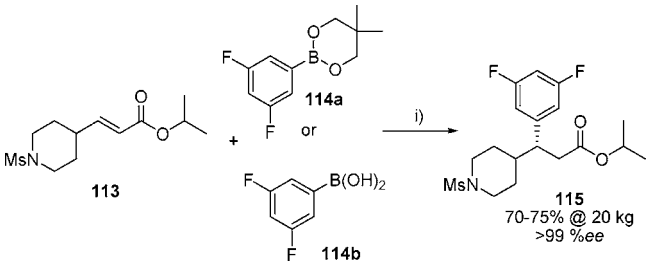
Scheme 20. Versatile Hayashi–Miyaura coupling[a]



[a]Reagents and conditions: i) $Rh(nbd)_2]BF_4$ (1.8 mol %), (*R*- or *S*)-BINAP (1.9 mol %), **110** (1.10 equiv), dioxane (16 vol), RT, 2 h then water (4 vol), TEA (1 equiv), **4** (1.0 equiv), RT, 18 h.

Scheme 21. Multikilogram Hayashi–Miyaura coupling[a]



[a]Reagents and conditions: i) $[Rh(COD)Cl]_2$ (1.0 mol %), (*R*)-BINAP (2.25 mol %), THF (2.8 vol), RT, 15 min then **113** (1.0 equiv), **114b** (1.35 equiv) and K_2CO_3 (1.35 equiv) in THF (7.8 vol) and ^{i}PrOH (1.0 equiv), 60 °C.

more consistent mixture allowing for better **C**ontrol. The final process was demonstrated on multiple 20 kg batches generating material in good yield and with almost complete stereoselectivity.

4. SUMMARY AND OUTLOOK

As stated in the opening section, the demanding constraints applied to large-scale processes have meant that a limited number of literature ACA and DCA methods have been demonstrated outside of the research laboratory. Classical methods of stereocontrol (substrate or auxiliary controlled) have proven successful using both "soft" and "hard" nucleophiles and multikilo syntheses have been described. In terms of catalytic stereocontrol, many classes of asymmetric catalysts have been utilised; organocatalysts, phase transfer catalysts, transition metal/ligand complexes and bifunctional bimetallic catalysts. Thus far, catalysis with organic molecules has been more successful at achieving ACA on larger scales and this is probably due to the (typically) plant-friendly conditions that can be used and the nonrequirement for potentially toxic or sensitive metal catalysts. We also should expect that, as the general areas of asymmetric organocatalysis and PTC mature in the coming years, further examples will be reported. Examples of large-scale ACA using "hard" organometallic nucleophiles are less prevalent; this is most likely due to the intrinsic nature of these reagents (high reactivity) and the conditions they often require (cryogenic temperatures and inert atmospheres). Hayashi–Miyaura coupling using rhodium catalysts and arylboronic acids has proven industrially useful, however, and some highly developed chemical processes have been communicated. For the remaining organometallic reagents (lithium, aluminium, zinc, magnesium), there are still challenges to be met in order to achieve large-scale ACA with synthetically useful alkyl units (e.g., methyl, vinyl); continued effort and enterprise from academic and process chemists will likely achieve this goal in the near future.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For examples of recent, industrial examples of asymmetric synthesis, see the Special Feature Section in *Org. Process Res. Dev.* **2011**, *15*(5), 1088–1211

(2) For a detailed discussion on 'SELECT' criteria for process development, see: Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gilmore, A. *Chem. Rev.* **2006**, *106*, 3002–3027.

(3) The term "Michael addition" has been employed in many ways to cover any and all types of conjugate- or 1,4-addition. For the purposes of this review, "Michael addition" is used in its original form to include the addition of enolate-type nucleophiles to α,β-unsaturated carbonyls.

(4) (a) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797–2799. (b) Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022–3024.

(5) Mase, T.; Houpis, I. N.; Akao, A.; Dorziotis, I.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775–6786.

(6) (a) Barnish, I, T.; Corless, M.; Dunn, P. J.; Ellis, D.; Finn, P. W.; Hardstone, J. D.; James, K. *Tetrahedron Lett.* **1993**, *8*, 1323–1326. (b) Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244–253.

(7) Barnes, D. M.; Ji, J.; Fickes, M. J.; Fitzgerals, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105.

(8) Magnesium has a recommended daily allowance (RDA) of around 400–500 mg/day for adult males and hence is of little toxicity risk.

(9) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959.

(10) Nickel is classified as a Class 1c metal with a Permitted Daily Exposure (PDE) limit of 2.6 μg/kg/day (i.e. of significant safety concern) by the EMEA; see: *Guideline on the Specification Limits for Residues of Metal Catalysts*, available online at www.ema.europa.eu.

(11) Ohshima, T.; Xu, Y.; Takita, R.; Shibisaki, M. *Tetrahedron* **2004**, *60*, 9569–9588.

(12) Abele, S.; Inauen, R.; Funel, J. A.; Weller, T. *Org. Process. Res. Dev.* **2012**, *16*, 129–140.

(13) For a review of PTC applications on large-scale, see: Maruoka, K. *Org. Process. Res. Dev.* **2008**, *12*, 679–697.

(14) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710–4711.

(15) Cragoe, E. J. Jr.; Woltersdorf, O. W. Jr.; Gould, N. P.; Pietruszkiewicz, A. M.; Ziegler, C.; Sakurai, Y.; Stokker, G. E.; Anderson, P. S.; Bourke, R. S.; Kimelberg, H. K.; Nelson, L. R.; Barron, K. D.; Rose, J. R.; Szarowski, D.; Popp, A. J.; Waldmant, J. B. *J. Med. Chem.* **1986**, *29*, 825–841.

(16) Scott, J. P.; Ashwood, M. S.; Brands, K. M. J.; Brewer, S. E.; Cowden, C. J.; Dolling, U. H.; Emerson, K. M.; Gibb, A. D.; Goodyear, A.; Oliver, S. F.; Stewart, G. W.; Wallace, D. J. *Org. Process. Res. Dev.* **2008**, *12*, 723−730.
(17) Lygo, B.; Allbut, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461−4464.
(18) Diisopropyl ether carries the EUH019 designator for elevated risk of peroxide formation.
(19) Lan, Q.; Wang, X.; Shirakawa, S.; Maruoka, K. *Org. Process Res. Dev.* **2010**, *14*, 684−686.
(20) For popular reviews in this area, see: (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304−308. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638−4660. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.
(21) Macmillan, D. W. C.; Paras, N. A. U.S. Pat. Appl. 2003/0236438 A1 2003.
(22) Holbrook, A. M.; Pereira, J. A.; Labiris, R.; McDonald, H.; Douketis, J. D.; Crowther, M.; Wells, P. S. *Arch. Intern. Med.* **2005**, *165*, 1095−1106.
(23) (a) Halland, N.; Jorgensen, K. A.; Hansen, T. Int. Pat. WO 03/050105 A2, 2003. (b) Halland, N.; Jorgensen, K. A.; Hansen, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955−4957.
(24) Xu, F.; Zacuto, M.; Yoshikawa, N.; Desmond, R.; Hoerrner, S.; Itoh, T.; Journet, M.; Humphrey, G. R.; Cowden, C.; Strotman, N.; Devine, P. *J. Org. Chem.* **2010**, *75*, 7829−7841.
(25) Valero, G.; Schimer, J.; Cisarova, I.; Vesely, J.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2009**, *50*, 1943−1946.
(26) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305−4309.
(27) (a) Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647−5651. (b) Amat, M.; Hidalgo, J.; Bosch, J.; Cantó, M.; Pérez, M.; Llor, N.; Mollins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074−3084. (c) Czibula, L.; Nemes, A.; Sebök, F.; Szántay, C. Jr.; Mák, M. *Eur. J. Org. Chem.* **2004**, *44*, 3336−3339. (d) Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, *12*, 2074−2076.
(28) For a recent and general review, see: (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, *9*, 1279−1300. For industrial applications, see: (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177−2250.
(29) For reviews, see: (a) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039−1075. (b) Thaler, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 645−648. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796−2823.
(30) For reviews, see: (a) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093−2105. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.
(31) Organolithium species are widely used for industrial applications, see: Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596−2616.
(32) Takashi, E.; Matsushita, H.; Kawakami, H.; Koseki, K. Eur. Pat. Appl. 0460413 A1, 1991.
(33) Martynow, J.; Krupa, M.; Leś, A.; Kutner, A.; Szelejewski, W. *Org. Process. Res. Dev.* **2004**, *8*, 846−851.
(34) Boulton, L. T.; Brick, D.; Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parkin, N.; Rhodes, R.; Ruecroft, G. *Org. Process. Res. Dev.* **2002**, *6*, 138−145.
(35) (A) Song, Z. J.; Zhao, M.; Frey, L.; Li, J.; Tan, L.; Chen, C. Y.; Tschaen, D. M.; Tillyer, R.; Grabowski, E. J. J.; Volante, R.; Reider, P. J. *Org. Lett.* **2001**, *3* (21), 3357−3360. (b) Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658−9667. (c) Frey, L.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U. H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 3120−3124. (d) Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1998**, 1651−1655.
(36) Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29* (35), 4411−4414.
(37) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376−1378.
(38) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358−7362.
(39) The following prices are representative (www.SigmaAldrich.com): 2 M Me_2Zn (~£500 per 100 mL); 2 M MeMgBr (~£40 per 100 mL); 2 M Et_2Zn (~£120 per 100 mL); 2 M EtMgBr (~£35 per 100 mL).
(40) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175−3182.
(41) Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* (16), 5834−5838.
(42) Lum, T.-K.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2008**, *10* (5), 761−764.
(43) Ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2007**, *9* (16), 3013−3015.
(44) (a) Hogan, P. J.; Powell, L.; Robinson, G. E. *Org. Process Res. Dev.* **2010**, *14*, 1188−1193. (b) Mahmood, A.; Powell, L.; Robinson, G. E. *Org. Process Res. Dev.* **2011**, *15*, 49−52. (c) Brazier, E. J.; Hogan, P. J.; Leung, C. W.; O'Kearney-McMullan, A.; Norton, A. K.; Powell, L.; Robinson, G. E.; Williams, E. G. *Org. Process Res. Dev.* **2010**, *14*, 544−552.
(45) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 906−910.
(46) Harutyunyan, S. R.; ben Hartog, T.; Guerts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824−2852.
(47) Arnold, L. A.; Naasz, R.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104−1105.
(48) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097−1100.
(49) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M. *J. Am. Chem. Soc.* **1998**, *120*, 5579.
(50) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10* (15), 3235−3238.
(51) Wallace, G. A.; Gordon, T. D.; Hayes, M. E.; Konopacki, D.; Fix-Stenzel, S. R.; Zhang, X.; Grongsaard, P.; Cusack, K. P.; Schaffter, L. M.; Henry, R. F.; Stoffel, R. H. *J. Org. Chem.* **2009**, *74*, 4886−4889.
(52) Brock, S.; Hose, D. J.; Moseley, J. D.; Parker, A. J.; Patel, I.; Williams, A. J. *Org. Process Res. Dev.* **2008**, *12*, 496−502.