Enamides: valuable organic substrates

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Enamides display a fine balance of stability and reactivity, which is now leading to their increasing use in organic synthesis. Enamides offer multiple opportunities for the inclusion of nitrogen based functionality into organic systems. Recent examples of these compounds as substrates are discussed in this article.

Introduction

Over recent years, an increasing level of interest in the use of enamide substrates has become apparent within the organic synthesis community, possibly a reflection on an ever increasing number of enamide syntheses that offer substrate versatility and *E*/*Z* control.[1,2]

Enamides feature noticeable nucleophilic reactivity by virtue of the enamine character yet are tempered by the electron withdrawing functionality upon the nitrogen centre, leading to significant chemical stability. However, these molecules often react akin to simple C=C bonds and offer further options for the incorporation of *N*-functionality into complex systems.

These two characteristics, coupled with recent improvements in their synthesis, has allowed for increased synthetic use. This review will cover some key transformations of enamides, enecarbamates, and enesulfonamides (Fig. 1) published in recent years and offer the reader contexts where enamides may be of synthetic value to their chemistry.

Enamides as nucleophiles

Enamides can be viewed as tuneable enamines and as such, it is no surprise that they participate in a number of interesting transformations with electrophiles. Groundbreaking work in this area originated from the Kobayashi laboratory,[3] who reported the first enantioselective use of enamides as nucleophiles in reactions with aldehydes under Cu-catalysis. This early work suffered from products being produced with low to medium levels of enantioselectivity.[4] In contrast, the use of imine electrophiles has allowed for the formation of β-amino imines using similar chiral Cu-catalyst systems that failed with simple aldehydes (Scheme 1).[5]

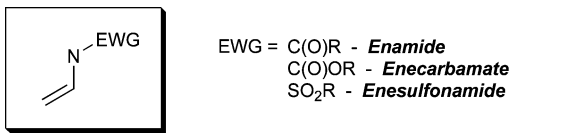
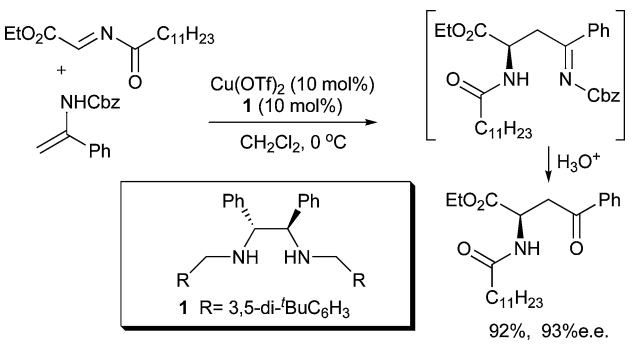


Fig. 1 Classes of "enamide".



Scheme 1 Enamide addition to glyoxalate imines.

The Kobayashi laboratory has since demonstrated the use of C_2 symmetric diamine ligands with a range of electrophiles and enamides as nucleophiles, promoted by Cu(II)-catalysts in conjunction with iminophosphonates for the enantioselective formation of phosphonic acid systems,[6] diazodicarboxylates for enantioselective α-aminations[7] and eventually demonstrated that some aldehydes (α-oxo aldehydes) will participate as useful electrophiles.[8] The Kobayashi group have once again demonstrated the synthetic utility of enamides in an enantioselective Michael reaction which forms, after hydrolysis, γ-keto malonates in good yield and selectivity with an example displayed in Scheme 2.[9]

Terada has reported that enamides are excellent substrates for chiral Brønsted acid promoted enantioselective additions to glyoxals. Binol based phosphonic acids have been utilised as catalysts for this purpose in an organocatalytic synthesis of β-hydroxy ketones (Scheme 3).[10]

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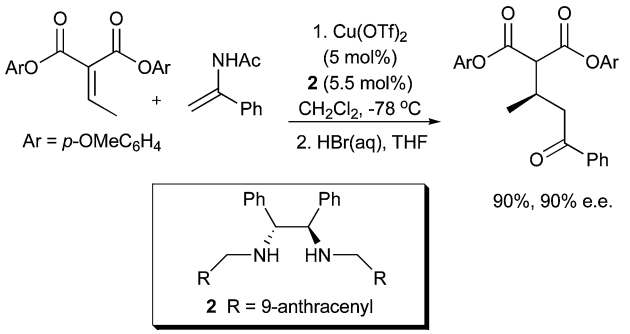
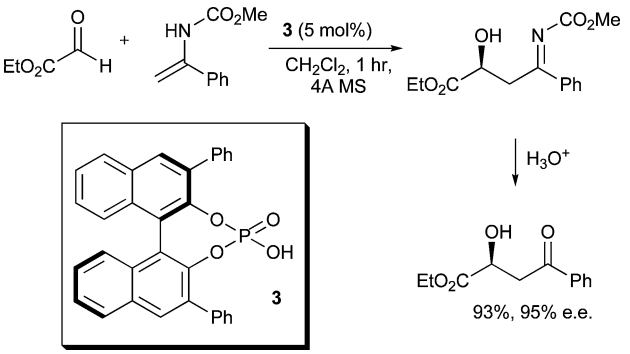
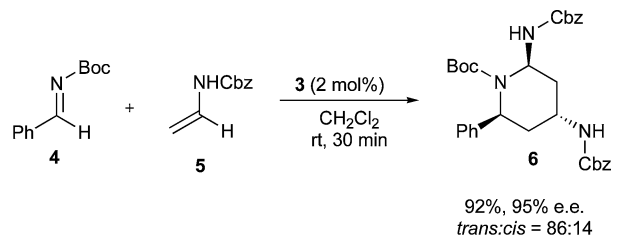


Scheme 2 Enantioselective enamide Michael reactions.



Scheme 3 Aza-ene reactions using enamides.

These initial findings have evolved into an impressive enantioselective synthesis of piperidines using aldimine **4** and enamide **5** (Scheme 4). In this instance, the β-amino imine product formed after the initial Mannich reaction of enamide **5** and imine **4** undergoes a subsequent nucleophilic attack by a second equivalent of enamide **5** followed by cyclisation to form the piperidine ring system **6**. Products of significant complexity are formed rapidly with excellent yields and enantioselectivities.[11]

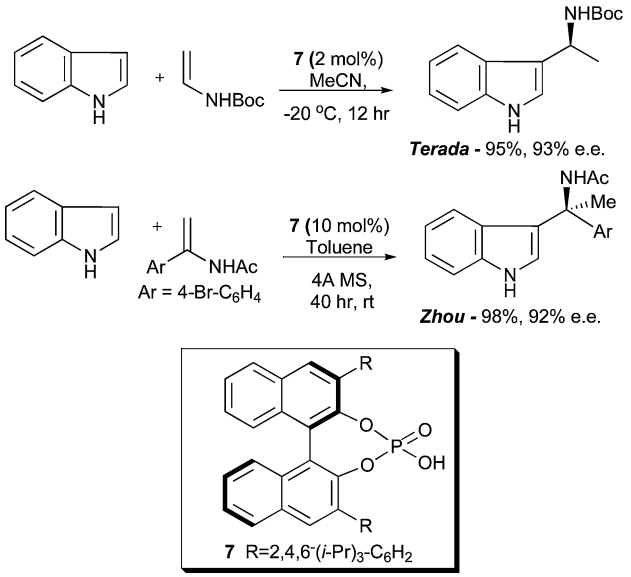


Scheme 4 An enantioselective cascade of enamides and imines.

Enamides as electrophiles

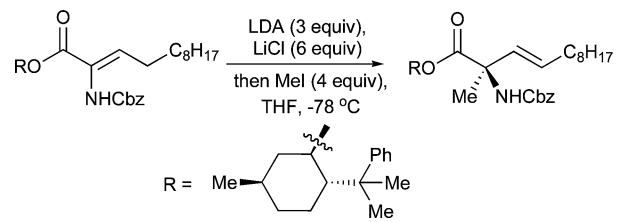
Recently the Terada and Zhou groups independently reported that chiral Brønsted acids can promote the conversion of enamides to chiral iminium ion electrophiles, which can subsequently participate in Friedel–Crafts reactions.[12] Furthermore, Zhou was able to exquisitely demonstrate that α-substituted enamides not only undergo this chemistry but do so with excellent levels of enantioselectivity and reaction efficiency (Scheme 5).[13]

The Marsden research group has reported the use of dehydroamino acid ester based enamides as substrates for a strong-base mediated deconjugative deprotonation. This procedure



Scheme 5 Alkylation of indole by enamide derived electrophiles.

forms amino ester enolates, which can be reacted with various electrophiles to form complex (*E*)-vinylglycines.[14] The use of chiral esters such as the 8-phenylmenthyl systems offer excellent diastereocontrol in this transformation (Scheme 6).[15]

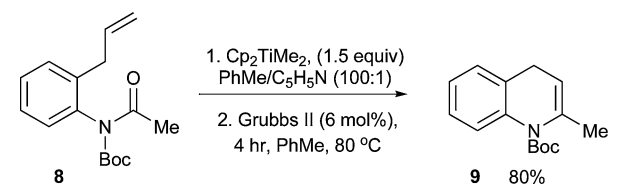


Scheme 6 Enamide alkylation *via* deconjugative enolisation.

Transition metal catalysed reactions

The one reaction that is well developed for enamide substrates is alkene hydrogenation. Substantial literature is available concerning the reduction of dehydroamino acid systems.[16,17] This chemistry will not be covered in this emerging area article.

Enamides can be viewed as attractive substrates in a number of transition metal mediated alkene transformations, especially in contexts where incorporation of nitrogen functionality is important. For example, the important ring-closing metathesis reaction has been applied to enamides allowing for the synthesis of cyclic enamides. Bennasar has demonstrated that enamides can participate in ring closing metathesis reactions (Scheme 7).[18] Indeed, this example is a one-pot Petasis-methylenation of **8**

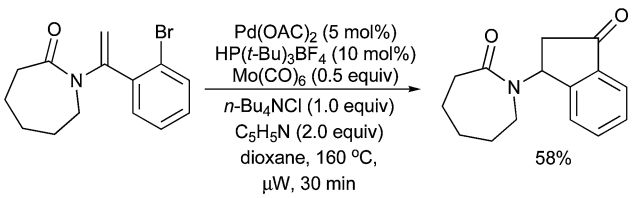


Scheme 7 Tandem methylenation–enamide ring closing metathesis.

followed by ring closing metathesis with the second generation Grubbs catalyst forming dihydroquinoline **9**.

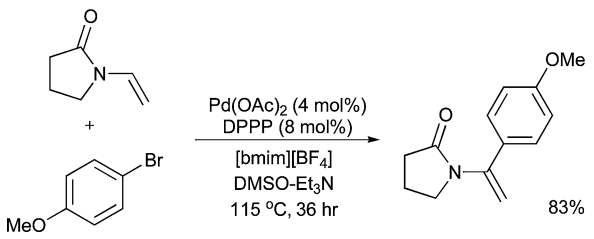
Additional recent demonstrations of this class of transformation have been reported by Evano as a key reaction in the total synthesis of the cyclopeptide paliurine[19,20] and by Overman who has also reported ring closing metathesis reactions of enamides in studies towards the synthesis of palau'amine.[21]

A second transformation that has been applied to enamide substrates is the Heck reaction. The Larhed group has reported a series of papers concerning the use of enamides in Heck processes. An indanone synthesis was reported that utilised enamides in a carbonylative microwave assisted Heck process with the notable use of the mild carbon monoxide source, $Mo(CO)_6$ (Scheme 8).[22]



Scheme 8 Enamides used in a carbonylative Heck reaction.

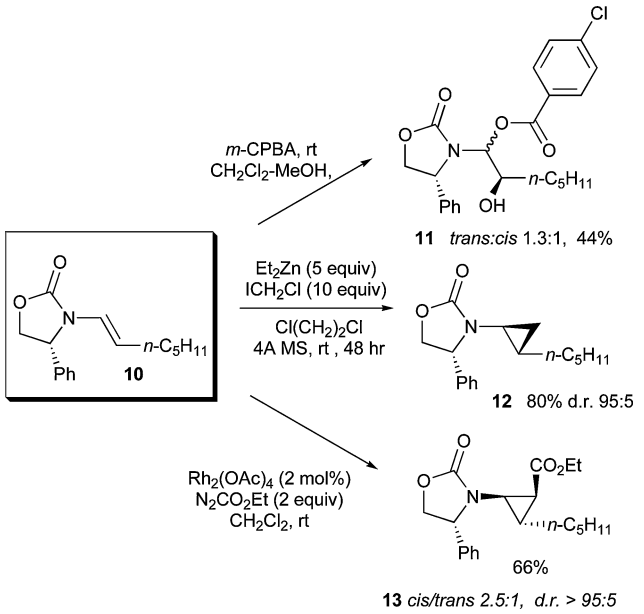
The Larhed group have also published an oxidative Heck arylation, which combines a coupling of boronic acids.[23] Xiao has demonstrated that ionic liquids are particularly good solvents for Heck reactions of enamides, often offering much improved regiocontrol (Scheme 9).[24]



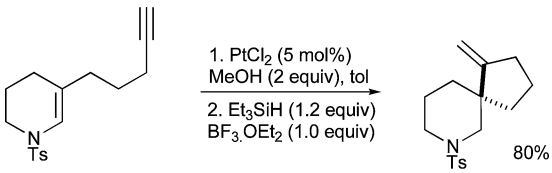
Scheme 9 Heck reaction of enamides in ionic liquids.

The Hsung laboratory have been key movers in exploring the synthetic value of enamide substrates. One of their first reports concerned the *m*-CPBA epoxidation of chiral oxazolidinone based substrates. For example, enamide **10** is observed to epoxidise followed by facile ring opening by *m*-chlorobenzoic acid and is believed to occur with *N*-assistance leading to a 1.3 : 1 anomeric aminal mixture of **11**. This observation suggests that the initial epoxidation occurs with high facial selectivity.[25] Subsequent work has focused upon cyclopropanation of chiral oxazolidinone enamides. Simmons–Smith[26] and Rh-catalysed[27] cyclopropanation methods have been examined to form **12** and **13** respectively. In particular, the Simmons–Smith cyclopropanation reaction is seen to be particularly diastereoselective relative to the Rh-catalysed example (Scheme 10).

Drake has reported an exciting transformation of cyclic enesulfonamides bearing pendant alkyne functionality. Under Pt(II)-catalysis, *spiro*-iminium systems are formed through alkyne activation.[28] Subsequent one-pot reduction with Et_3SiH provides the *spiro*-piperidine in good yield. A number of polycyclic ring systems are accessible offering a versatile route to a number of alkaloid frameworks (Scheme 11).



Scheme 10 Hsung's work with enamides.

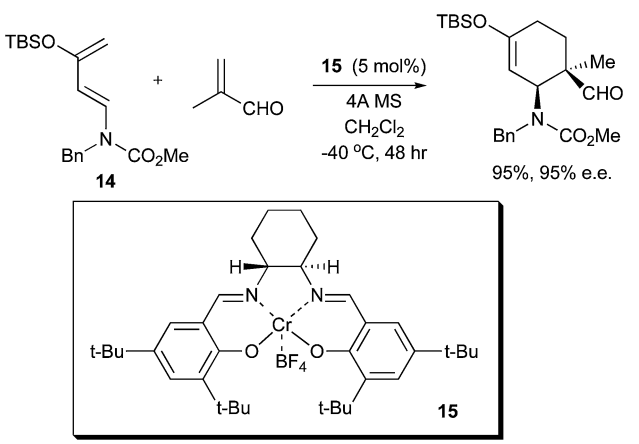


Scheme 11 Pt(II)-catalysed *spiro*-cyclisations.

Pericyclic reactions

In recent years there has been an increasing use of enamide substrates in pericyclic reactions. Indeed, examples of cycloaddition, sigmatropic and electrocyclic chemistry have all been reported. In many instances, the C_{sp2}–N bond is transformed to a C_{sp3}–N bond as a result of the pericyclic reaction allowing the formation of new nitrogen stereocentres and an overall increase in molecular complexity.

Rawal reported a highly efficient and stereoselective Diels–Alder reaction using the conjugated enamide **14** as the reactive diene (Scheme 12).[29] The reaction is promoted by Cr-salen complex **15**

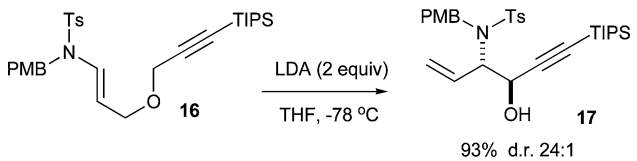


Scheme 12 Enamide participation in Diels–Alder reactions.

and yields synthetically useful cyclohexenyl carbamates in high eneantiomeric excess.

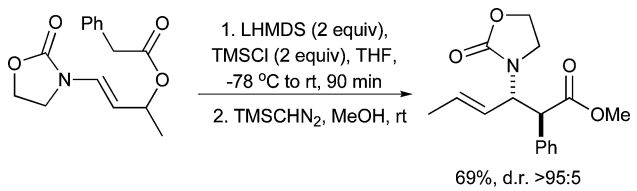
Further interesting uses of enamide substrates in the Diels–Alder reaction have come from Dujardin who has utilised *N*-vinyl oxazolidinones in hetero Diels–Alder reactions to give amino deoxyglycosides,[30] and *N*-vinyl oxazolidithiones.[31] *Exo*-selective Diels–Alder reactions of vinyl azepine diene substrates have been reported as an entry to the stenine framework.[32]

Meyer reported the first example of a sigmatropic rearrangement that incorporated an enamide moiety. In this example enamide **16** was transformed to amino alcohol **17** by means of a [3,2]-Wittig rearrangement. This reaction is seen to be a highly diastereoselective entry to 1,2-amino alcohol derivatives (Scheme 13).[33]



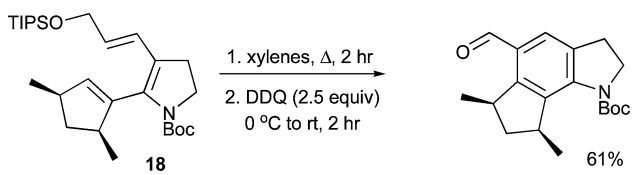
Scheme 13 [2,3]-Wittig rearrangements of enamides.

Carbery has recently reported the first use of enamides as substrates for the Ireland–Claisen [3,3]-rearrangement (Scheme 14). In this instance secondary enamido-allylic esters rearrange *via* the silyl ketene acetal to β-amino acid products. The rearrangement was highly diastereoselective for phenylacetate substrates.[34]



Scheme 14 [3,3]-Ireland–Claisen rearrangement of enamides.

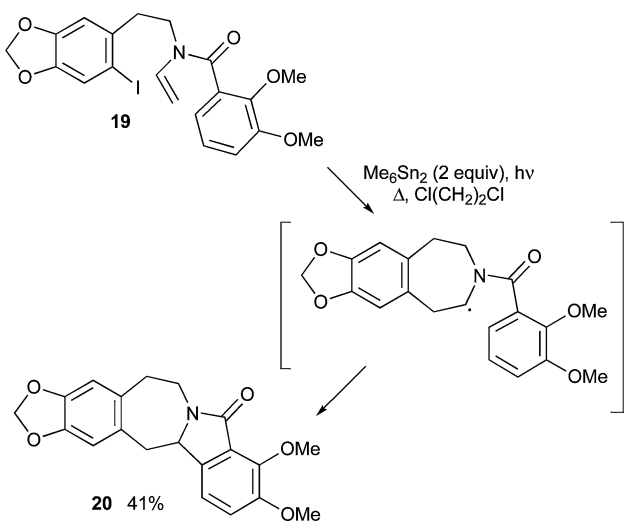
Enamides have also found themselves amenable to electrocyclic transformations. Funk has utilised 2,3-pyrroline **18** in a thermal 6π-electrocyclic ring closure, which ultimately allowed efficient access to the substituted indole framework seen in the trikentrin alkaloids (Scheme 15).[35] Funk has further shown that this strategy is applicable to the welwistatin,[36] dragmacidin E[37] and nakadomarin A[38] natural product skeletons.



Scheme 15 Enamides in electrocyclisations.

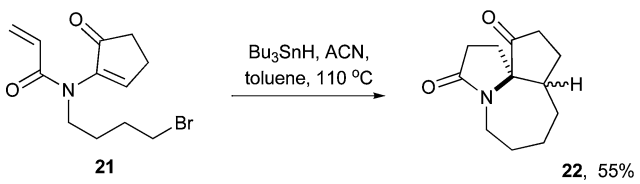
Radical reactions

In recent years there have been a number of reports detailing the utility of enamides in radical based transformations. In particular Ishibashi has clearly shown the synthetic value of these enamide substrates through the synthesis of lennoxamine **20**. Enamide **19** is observed to undergo a regioselective 7-*endo* cyclisation followed by subsequent homolytic aromatic substitution (Scheme 16). This single-pot process allows for the isolation of lennoxamine in 41%.[39]



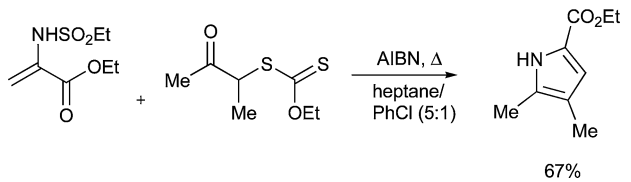
Scheme 16 Ishibashi's lennoxamine synthesis.

The Ishibashi group have recently further demonstrated the value of enamide substrates in radical reactions by accomplishing syntheses of (±)-stemonamide and (±)-isostemonamide where the skeleton is formed through a key enamide radical reaction. In this instance, substrate **21** undergoes a double radical cascade cyclisation initiated by 1,1′-azobis-cyclohexanecarbonitrile and terminated by Bu_3SnH (Scheme 17). Diastereomeric tricycles **22** are formed in respectable yield, albeit in a 1 : 1 ratio. Further elaboration of these tricycles allowed for succint syntheses of these natural products.[40]



Scheme 17 A tandem radical cyclisation entry to the stemonamide skeleton.

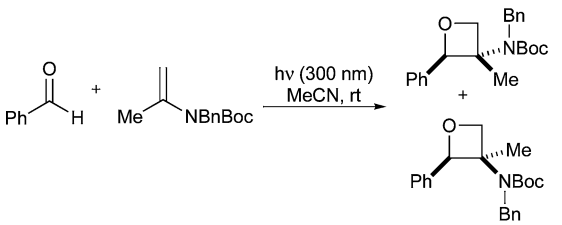
Zard has described a free-radical based synthesis of pyrroles that relies upon the use of ethyl pyruvate derived enesulfonamide substrates as α-keto radical acceptors (Scheme 18). The γ-keto imines that form are non-isolable, immediately cyclising to pyrroles.[41]



Scheme 18 Pyrrole formation from enesulfonamides.

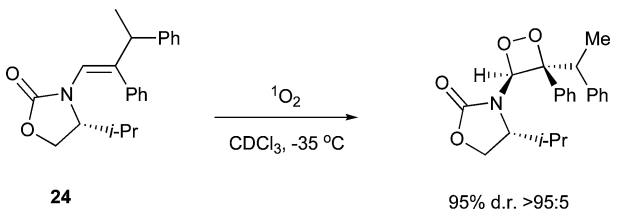
Photochemical reactions

The area of photochemistry has seen the use of enamides as substrates in the Paterno–Büchi photochemical reaction.[42] Bach has demonstrated that enecarbamates participate particularly well, forming amino oxetanes **23** in good yield with significant diastereoselectivity (Scheme 19).



Scheme 19 Enamide Paterno–Büchi reaction.

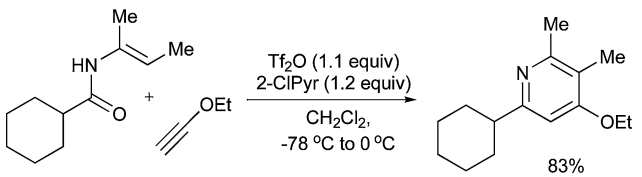
Adam has published a substantial amount of work in the area of enecarbamate photochemical oxidations. For example, enecarbamte **24** undergoes a stereoselective [2 + 2] cycloaddition with singlet oxidation (Scheme 20). The selectivity is observed to be controlled by the oxazolidinone stereochemistry as opposed to the distal stereocentre of the substrate. The same group have also studied the selectivity displayed by enecarbamtes to either photochemical $^1O_2$ or ozone reactions[43] and $^1O_2$ ene-reaction or $^1O_2$ [2 + 2] cycloadditions.[44]



Scheme 20 Singlet oxidation reaction of enecarbamates.

Heterocycle syntheses

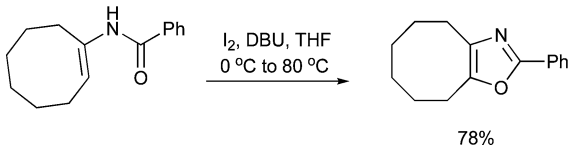
Over recent years, the applicability of enamides to heterocyle synthesis has been well demonstrated. Movassaghi has reported a new and versatile synthesis of pyridines. In this reaction enamides are converted to *N*-vinyl iminium triflates through the action of triflic anhydride, subsequently reacting with electron rich hetero-substituted alkynes or alkenes to form pyridines (Scheme 21).[45]



Scheme 21 Pyridine synthesis utilising enamides.

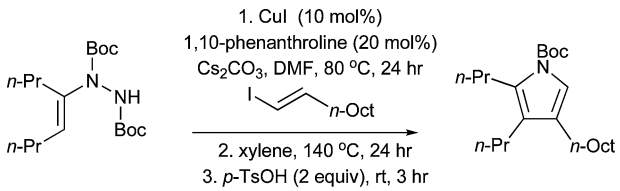
This research group has also achieved an analogous transformation using nitriles, replacing the ynol ethers, as a versatile entry to pyrimidines.[46]

A number of reports have come from the Buchwald group, which demonstrate recent advances in both copper catalysed alkene amination but also new reactivity of enamides. For example, enamides form oxazoles when heated in the presence of iodine and DBU in good yields, with a good level of substrate scope (Scheme 22).[47]



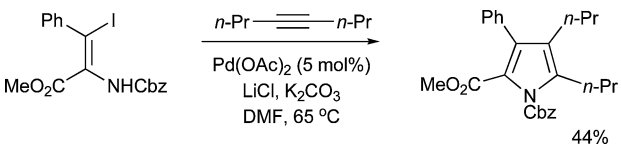
Scheme 22 Enamide based synthesis of oxazoles.

The same research group has also reported a new synthesis of highly substituted pyrroles with impressive levels of substitution control. Di-*N*-bochydrazine undergoes a selective Cu(I)-catalysed mono amination followed by a sequential second Cu(I)-catalysed amination. The resulting hydrazine bisenamide then undergoes a [3,3]-sigmatropic rearrangement. This sequential amination–rearrangement protocol allows for the controlled introduction of functionality at all positions (Scheme 23). A similar transformation for the preparation of pyrroles that relies on amination has also been reported by Buchwald.[48]



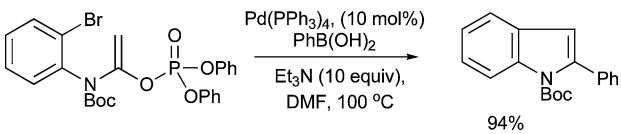
Scheme 23 Pyrrole formation.

A complementary synthesis of pyrroles has been reported from workers at Wyeth Research that takes inspiration from the "Larock Indole Synthesis". $Pd(OAc)_2$–LiCl catalysed reaction between iodoenamides and alkynes provides access to complex pyrroles with good control and yield (Scheme 24).[49]



Scheme 24 Iodo enamide route to pyrroles.

Fuwa and Saski have recently developed a versatile synthesis of 2-aryl iodoles and indolines centred upon the utility of α-phosphoryloxy enamides (Scheme 25).[50] The procedure benefits from impressive simplicity and once again displays the value and versatility of enamides in organic synthesis.



Scheme 25 Tandem reactivity in the preparation of indoles.

Conclusions

In recent years, a number of reliable and efficient syntheses of enamides have allowed their synthetic value to be realised. Enamides are now having their utility demonstrated in a range of reactions including pericyclic, ionic and radical transformations. Enamides offer themselves as useful substrates through two key aspects. Firstly, their stability relative to enamines allows them to be readily handled and tailors their reactivity through alteration of the electron withdrawing group upon the nitrogen. Secondly, the change of hybridisation of the carbon centre bonded to the enamide carbon allows for the controlled increase in complexity without the requirement of introducing nitrogen directly during key reactions.

Notes and references

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