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The base-catalysed Tamura cycloaddition reaction: calculation, mechanism, isolation of intermediates and asymmetric catalysis†

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A combined experimental and computational investigation has revealed that the base-catalysed Tamura cycloaddition between homophthalic anhydride and activated alkenes/alkynes – a reaction previously thought of as a Diels–Alder type process – proceeds *via* a stepwise mechanism involving conjugate addition and ring closure; which allowed the first catalytic asymmetric α-substitution reactions to be demonstrated with up to >99% ee.

In 1981[1,2] Tamura *et al.* reported that homophthalic anhydride (**1**) reacts with either activated alkenes or alkynes in aromatic solvents under reflux (Fig. 1A) to afford α-naphthols of general type **4**, in a highly regioselective manner. Later base-promoted variants of the process were developed which allowed reaction under milder conditions with greater efficiency.[2–6] The process has found considerable utility in the syntheses of medicinally relevant polycyclic aromatic natural products,[4] with the rapid construction of the core of Lactonamycin[5] and the total synthesis of the anti-tumour metabolite Dynemycin A[6] (*i.e.* **5** and **6** respectively, Fig. 1B) involving a homophthalic anhydride conjugate base (depicted by the authors as enolates **7**) serving as examples.

Tamura proposed three distinct mechanistic pathways (Fig. 1C).[7] Pathway A comprised a Diels–Alder cycloaddition between the homophthalic anhydride–enol isomer **1a** to a dienophile such as **3** to yield **8**, followed by decarboxylation to **9** and loss of molecular hydrogen. Pathway B involved a stepwise Michael-type addition of the enol isomer **1b** to **3** to afford adduct **10**, followed by an intramolecular cyclisation and subsequent decarboxylation/oxidation of **11**. Pathway C was suggested to proceed *via* a thermal decarboxylation of **1** to give the cyclobutanone derivative **1c** followed by ring opening to **12** and a concerted 4+2 cycloaddition with **3**; with oxidation/tautomerisation of **13** (a tautomer of **9**) to **4** following.

In the seminal study,[1] Tamura first ruled out Pathway C, as **1c** was not observed after **1** was subjected to prolonged heating; despite the generation of **1c** from **1** having been previously reported to occur at high temperatures[8] in the literature.

Tamura suggested[1] Pathway A was the most plausible – as thermal conditions may provide access to the least stable enol tautomer of homophthalic anhydride (*i.e.* **1a**), which, in the presence of maleimide **14** forms the bis-cycloadduct **16**. This was rationalised in terms of a Diels–Alder reaction between enol intermediate **15** (an analogue of **9**) and **14** (Fig. 1D).

To investigate the plausibility of Pathway B, Tamura reacted lithium enolate **17** (Fig. 1E) with known Michael acceptors of general type **18**. No reaction was observed from −78 °C to room temperature. Sodium enolate **19** – which cannot exist in a dienol form such as **1a** – was inert towards dienophile **20** even under forcing conditions.[9] While Tamura could not completely discount Pathway B, he favoured Pathway A – which became the 'accepted' mechanism. The process has been referred to as a 4+2 cycloaddition[11] and 'The Tamura Diels Alder reaction' since,[5] and while Tamura's mechanistic picture has not been challenged, concerns regarding the cycloaddition's synchronicity have appeared in the literature,[2,5,10]

For the synthetic potential of this reaction to be realised (enantioselective variants of this reaction have recently appeared[12]), a clarification of the mechanism is required. Herein, we report a joint experimental–computational investigation of the base-mediated analogue of the cycloaddition reaction originally used by Tamura to support a Diels–Alder mechanistic hypothesis (see Fig. 1D). We show that the amine-catalysed reaction of maleimide **21** with **1** proceeds *via* a stepwise process akin to Tamura's Pathway B involving conjugate addition to form **22** followed by ring-closure to **23**.

We began by examining the reaction between two substrates Tamura had reported underwent smooth cycloaddition: homophthalic anhydride (**1**) and *N*-phenyl maleimide (**14**). To maximise the chances of observing intermediates in these cycloadditions an

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‡ X-Ray crystallography facility.

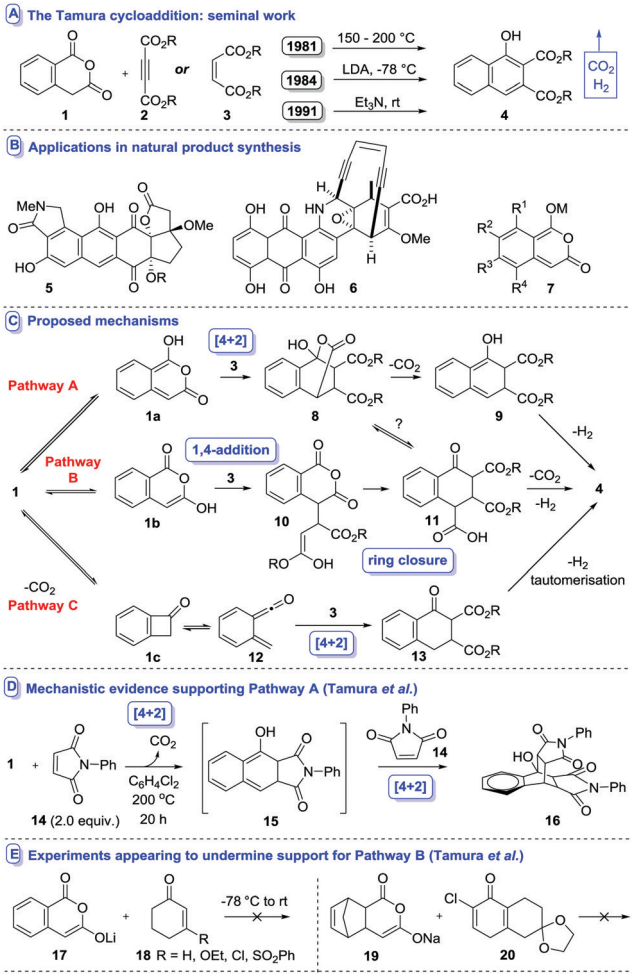
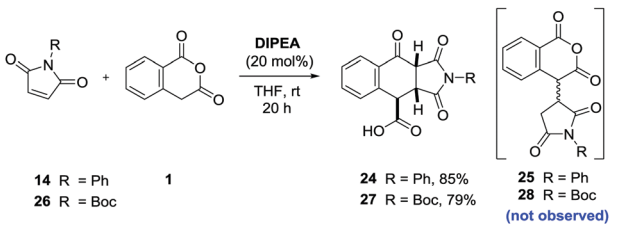


Fig. 1 The Tamura cycloaddition reaction.

amine catalyst[13] was employed to allow cycloaddition to occur under milder conditions less conducible to decarboxylation events.

The reaction between **1** and **14** proceeded smoothly in the presence of catalytic *N*,*N*-diisopropylethylamine (DIPEA) in THF – affording the fused tricyclic product **24** as a single diastereomer in high yield after 20 h (Scheme 1). The product from the conjugate addition of the enol form of **1** to **14** (*i.e.* **25**) was not discernible by ^{1}H NMR spectroscopic analysis of either the crude reaction mixture or during reaction monitoring. The absence of **25** could be explained by an inconveniently rapid (on an NMR timescale) cyclisation step to form **24**. In an attempt to stabilise the putative



Scheme 1 Cycloaddition between **1** and **14** in the presence of DIPEA.

conjugate addition product, we introduced an electron-withdrawing substituent on the maleimide nitrogen atom. Unfortunately, when *N*-Boc maleimide **26** was reacted under the same conditions to yield **27**; again the expected adduct **28** was not observed (Scheme 1).

A DFT theoretical study (wB97xD/6-311++g(d,p), PCM-THF conditions at 298 K) of the cycloaddition between **26** and **1** (Fig. 2) was next carried out.[14] In order to simplify the calculations, the free-energy profile was calculated with trimethylamine (TMA) as the base. We first considered and rejected a scenario involving Pathway C – due to a calculated energy barrier to the initial extrusion of carbon dioxide at room temperature of >100 kcal mol^{-1}.

In investigating Pathway A – involving the complex **1a-26** – we first sought to locate a [4+2] cycloaddition transition state (TS) by constraining the distances between atoms involved in the concerted mechanism and then taking the optimised constrained structure as an initial estimate for a full optimisation without any constraints. Every calculation led us to the corresponding complex before conjugate addition: a concerted Diels–Alder type TS was elusive. In order to describe the free-energy profile corresponding to both Pathways A and B, the first minima to be obtained (after deprotonation of the anhydride **1** by the base) were those of the trimethylammonium enolates[15] in complex with **26** (Fig. 2A); which revealed the enolate associated with Pathway B (*i.e.* **1b-26**) to be 3.5 kcal mol^{-1} more stable than the corresponding enolate **1a-26** required for Pathway A to operate (Fig. 2B). Thus, the first reaction corresponding to the enolisation process is more

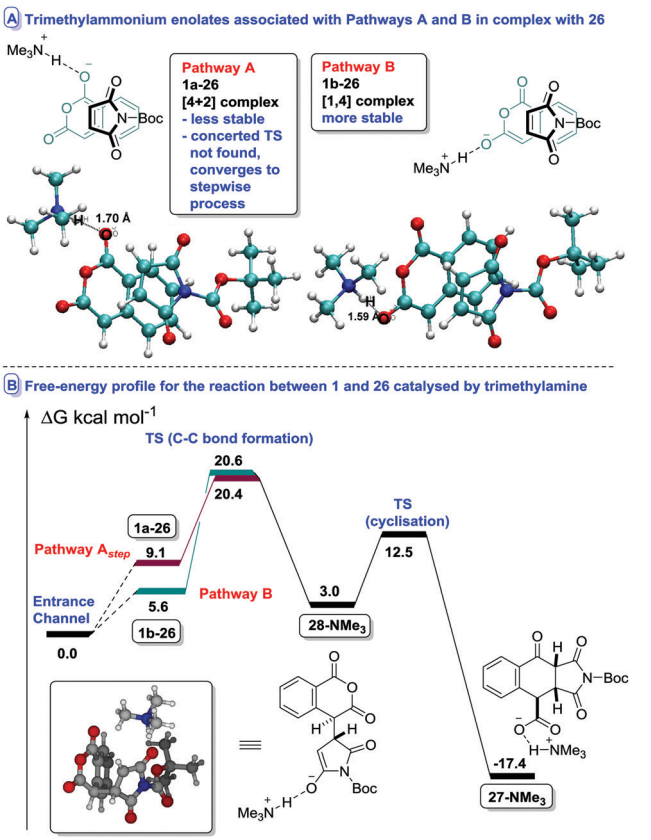


Fig. 2 Free-energy profile for complexes formed along Pathways A, B.

favourable for the enolate **1b-26** (Fig. 2A). Therefore, for the studied reaction, both Pathways A and B are likely to be stepwise addition mechanisms which begin with a rate-determining Michael-type addition of the anhydride-derived enolate (after deprotonation) to the dienophile (*i.e.* **1a-26** and **1b-26** reacting, respectively).

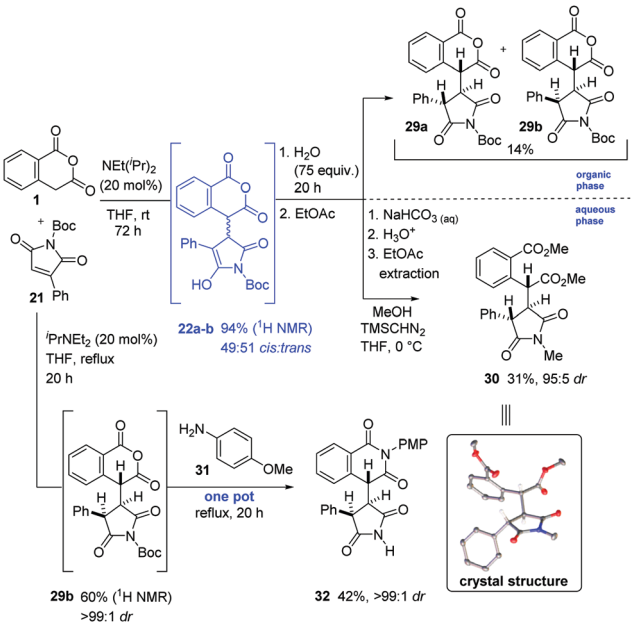
An examination of the free-energy profile (Fig. 2B) leads to the conclusion that stepwise Pathway B involves more facile enolate formation, yet the overall barrier to C–C bond formation is similar to that associated with a competitive stepwise variant of Tamura's Pathway A (labelled Pathway A_{step} in Fig. 2B) as they differ (in the main) by the location of the trimethylammonium ion. Pathway B – which possesses the lower energy enolate–dienophile complex **1b-26**, then proceeds to form the adduct **28-NMe$_3$** (Fig. 2B), which then cyclises (essentially irreversibly under these conditions) to the stable product **27-NMe$_3$**. Thus, while it appears that a Diels–Alder mechanism cannot be utilised to rationalise the base-mediated reaction, the assertion by Tamura that a less stable enol (*i.e.* **1a**) could participate in the process certainly has merit.

Accordingly, we also carried out a DFT on the first reaction step involving **14** and either **1a** or **1b** under Tamura's original thermal conditions (Fig. 1D). At the higher temperature, both a TS for the cycloaddition (Pathway $A_{concerted}$) and the conjugate addition (Pathway B) were located. The complex between **1a** and **14** (required for the concerted pathway) is 10.6 kcal mol^{-1} less stable than the corresponding complex involving **1b** in an endo approach and 9.7 kcal mol^{-1} less stable in an *exo* alignment. Interestingly however, the overall barrier to the C–C bond forming steps from the starting materials associated with Pathway A is now 1.0 kcal mol^{-1} lower than the corresponding barrier to conjugate addition (Pathway B). Thus it would seem that under forcing thermal conditions in the absence of base, that both pathways are feasible despite the overwhelming dominance of the complex involving enol **1b** over its counterpart **1a** (with which it is presumably in equilibrium with *via* **1**, see ESI†).

The 3 kcal mol^{-1} energy difference between the starting materials and **28-NMe$_3$** (Fig. 2B) prompted us to attempt to stabilise the enolate through the introduction of a phenyl unit – with the aim of detecting the Michael-type adduct (Scheme 2).[15] The base-mediated reaction involving **21** is a considerably slower process, however, after 3 d, ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed full conversion to the Michael adduct as its enol tautomer (*i.e.* **22a–b**) as a 1 : 1 mixture of diastereomers.

Adduct **22** proved remarkably resistant to hydrolysis: after addition of a large excess of water followed by EtOAc and extraction with aqueous $NaHCO_3$, significant levels of the diastereomeric keto tautomers **29a–b** (separable by chromatography) remained in the organic phase. The ^{1}H and ^{13}C NMR spectra of **29a–b** were unambiguous, however only fragments post-hydrolysis and decarboxylation could be detected by mass spectrometry. Therefore the hydrolysed carboxylate products in the aqueous phase were protonated and esterified with $TMSCHN_2$, which allowed the isolation of the adduct **30** with excellent dr.

In an attempt to force **22** to cyclise, the reaction was repeated in THF at reflux (Scheme 2). The keto form of the



Scheme 2 Isolation of Michael adducts **29a–b**.

Michael adduct was generated (*i.e.* **29b**) after 20 h. This was trapped for characterisation in a more straightforward fashion after the addition of *p*-anisidine (**31**) – which first ring opens the anhydride and then forms the imide **32** as a single diastereomer after heating.

The observed reluctance of **22** to cyclise was next investigated computationally. We carried out a study of the amine-catalysed reaction (Pathway B only) involving **1** and **21**. Unexpectedly, the calculated free-energy profile predicted that cyclisation should be a facile process for both diastereomers (**22a–b**, ESI,† Fig. S2) – in stark contrast with the experimental data. Upon inspection of the calculated TS for the cyclisation of the conjugate base of **22b** catalysed by NMe_3 (*i.e.* **33**, Fig. 3); it can be seen that the ammonium ion is located between the reacting anhydride and enolate and facilitates charge transfer by hydrogen-bonding. All attempts to obtain the same TS with protonated DIPEA positioned between both oxygen atoms (*i.e.* **34**) failed. We posited that while the trimethylamine base is sufficiently small to be straddled by the closing functionalities when protonated, the larger DIPEA used in the experimental study experiences steric clashes with the reacting functional groups of sufficient magnitude to prevent cyclisation.

The fortuitous initial decision to choose NMe_3 as a base in the DFT study now provided an opportunity to validate the

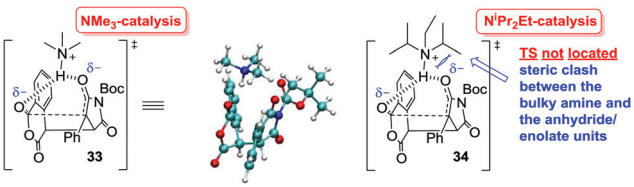
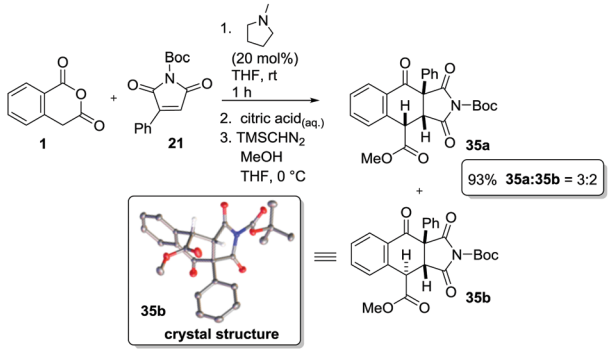


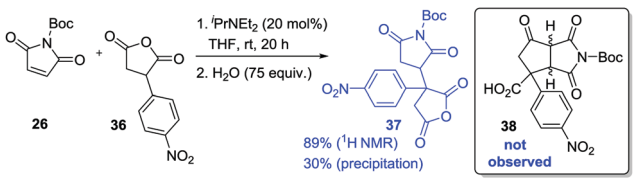
Fig. 3 Transition states associated with the cyclisation step.



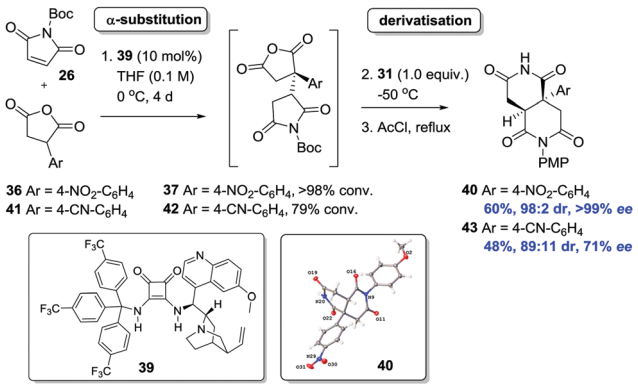
Scheme 3 Cycloaddition catalysed by *N*-methylpyrrolidine.

calculated pathway experimentally. Calculations indicated that DIPEA failed to promote the cyclisation reaction primarily for steric reasons, so use of an amine base of similar size to NMe_3 should have led to the calculated cyclised keto-acid product. Gratifyingly, exchange of DIPEA for *N*-methylpyrrolidine (Scheme 3) in the reaction between **1** and **21** led to quantitative cyclisation after 1 h. Liberation of the amine-bound carboxylic acids followed by extraction afforded a mixture of diastereomers. Derivatisation by esterification with $TMSCHN_2$ allowed the separation of the diastereomers **35a** and **35b** (with retention of dr) in a combined isolated yield of 93%.

We were also interested in evaluating the reactivity of other enolisable anhydrides – in particular those in which the formation of a dienol species such as **1a** is not possible. *p*-Nitrophenylsuccinic anhydride (**36**) was reacted with **26** in the presence of catalytic DIPEA – smoothly leading to **37** as a single diastereomer (Scheme 4). An attempt to derivatise by hydrolysis caused **37** to precipitate as a white solid. Interestingly – mirroring



Scheme 4 Amine-catalysed α-substitution of **36**.



Scheme 5 Catalytic asymmetric α-substitution of arylsuccinic anhydrides.

the situation observed using **1** – the fused bicyclic product **38** was not observed. This represents the first example of a catalytic α-substitution reaction involving anhydride enolisation under mild neutral conditions.

These findings opened a route to the organocatalytic generation of enantioenriched chiral anhydride electrophilic synthetic building blocks of considerable potential utility. An extensive catalyst screen identified the highly modified alkaloid derivative **39** as a promoter that could mediate the addition of the prototype anhydride **36** to **26** to form **37**, which was then derivatised for analysis as the bicycle **40** in near perfect enantio- and diastereocontrol (Scheme 5). The *para*-cyano variant **41** was also amenable to the transformation – yielding product **43** *via* adduct **42** in 71% ee and *ca.* 9 : 1 dr.

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Conflicts of interest

There are no conflicts to declare.

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