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Asymmetric Catalysis

Highly Enantio- and Diastereoselective Catalytic Asymmetric Tamura Cycloaddition Reactions

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Abstract: The first broad-scope catalytic asymmetric Tamura cycloaddition reactions are reported. Under the influence of anion-binding bifunctional catalysis a wide range of α,β-unsaturated *N*-trityl imines undergo reactions with enolisable anhydrides to form highly synthetically useful α-tetralone structures with excellent enantio- and -diastereocontrol. In stark contrast to the previous literature benchmarks, doubly activated or highly electron deficient alkenes are not required. A facile two-step, high yielding sequence can convert the cycloadducts to α-halo-ketones (challenging to generate catalytically by other means) with the net formation of two new C–C bonds and three new contiguous stereocentres with exquisite stereocontrol. A DFT study has provided insight into the catalyst mode of action and the origins of the observed enantiocontrol.

The Tamura reaction between homophthalic anhydride (**1**) and the activated alkyne **2** followed by loss of CO_2 and aromatisation at high temperature to give naphthol **3** was discovered in 1981 (Figure 1 A).[1] Shortly after, it was found that, in the presence of base, the reaction occurs under milder conditions with doubly activated alkene substrates such as **4**, to give the chiral adduct **5**.[2,3] Despite the Tamura cycloaddition finding application in the construction of the cores of natural products such as (inter alia) anthraquinone antibiotics,[2] lactonamycin[4] and dynemycin A,[5] its potential as a C–C bond and stereocentre-forming tool has been considerably stymied by the dearth of catalytic asymmetric variants.

The first of these[6] (which was reported in 2014) is highly enantio- and diastereoselective but can only be utilised for the formation of 3,3-spirooxindole products. A second, more recent methodology involves the reaction of α-alkyl-β-nitrostyrenes with **1**.[7] This possesses the advantage of using a singly activated electrophile, at the cost of a narrow substrate scope and a highly variable level of control over the stereocentres formed. A broad-scope catalytic asymmetric methodology for highly enantio- and diastereoselective Tamura reactions, which could produce malleable substituted chiral α-tetralones (a unit prevalent in a wide range of natural products, pharmaceuticals and molecules of medicinal and agrichemical interest,[8] of which rishirilide B[8c] and doxycycline[8e] are exemplary), remains well beyond reach.

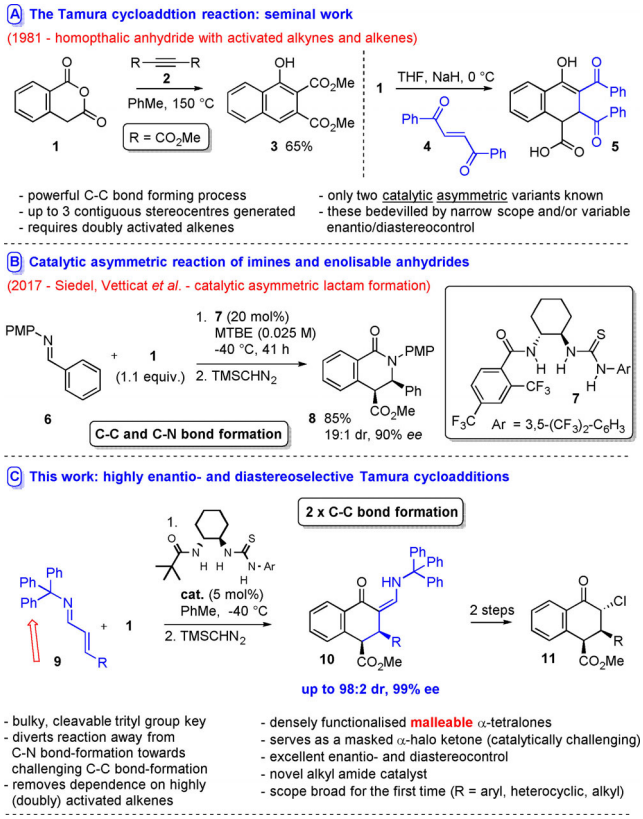

Figure 1. The Tamura cycloaddition reaction and related lactam generation.

In the 1990s, Bulgarian researchers[11] showed that if an α,β-unsaturated imine electrophile incorporated a bulky *N*-substituent, the reaction between **1** and α,β-unsaturated imines could be (partially) diverted away from the Mannich process and towards 1,4-conjugate addition. However, yields and/or

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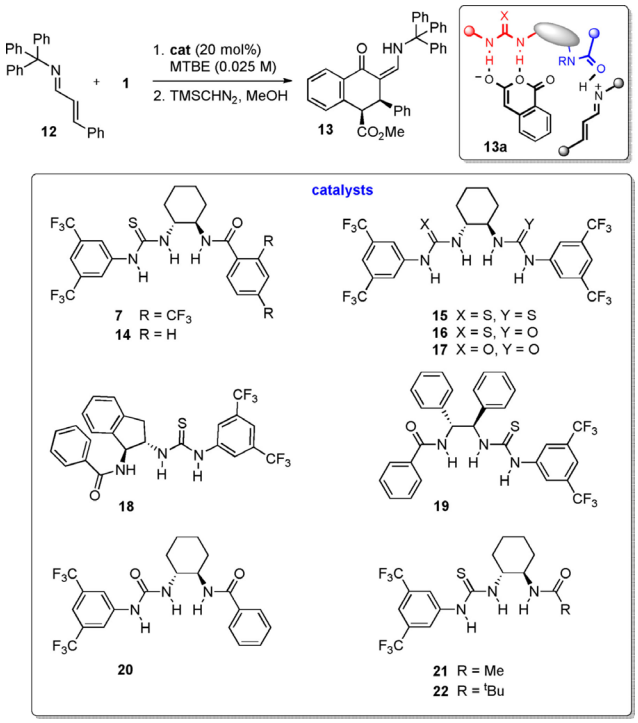
diastereocontrol were usually poor.[12] We postulated that if this process could be controlled, then Tamura reactions of considerably broader scope involving readily available, singly activated substrates (i.e., not requiring restrictive substitution at both alkene termini) could be brought into the orbit of asymmetric catalysis. Herein, we report the first such broad-scope Tamura cycloaddition reactions involving *N*-trityl imines of general type **9** and anhydrides such as **1** to form stable, densely functionalised α-tetralones **10** with excellent diastereo- and enantiocontrol using an improved, readily prepared thiourea catalyst (Figure 1 C).[13] The reaction is unique in that it constructs the tetralone core with control over two new stereocentres in a modular way,[14] in addition to generating a highly versatile enaminone vinylogous amide (synthetic building blocks for heterocyclic- and target-oriented synthesis of the first rank),[15] which we demonstrate can be readily converted to the α-haloketone **11**.

We began with the reaction between anhydride **1** and the cinnamaldehyde-derived *N*-trityl imine **12**[16] at ambient temperature in MTBE in the presence of Seidel's optimum catalyst (i.e., **7**, entry 1, Table 1). The challenge associated with developing the [1,4]-cycloaddition process (relative to the [1,2]-Castagnoli chemistry) is underlined by the formation of **13** with 32% *ee* (full conversion of **1**) and 3:1 d.r. in favour of the *syn*-diastereomer under identical conditions to those where **7** had been reported to mediate the generation of lactam **8** with 88% *ee* and 19:1 d.r. A solvent screen identified toluene as a superior solvent for the reaction, which marginally improved both enantio- and diastereocontrol simultaneously (Table 1, entries 2–6); however, stereocontrol remained some way short of synthetically useful levels. Thus, a redesign of the catalyst system was required.

Somewhat surprisingly, removal of the electron-withdrawing groups (which were important factors in achieving enantiocontrol in Seidel's study) from the catalyst's benzoylamide unit improved product enantioselectivity considerably (catalyst **14**, Table 1, entry 7). Nagasawa-type systems,[17] which are highly useful in anion-binding-mediated enantioselective acyl transfer[18] but were less effective asymmetric catalysts in the Castagnoli chemistry,[9] served comparatively well here, catalysing reactions with 49–80% *ee* and up to 70:30 d.r. (entries 8–10). Of most interest was the observation that, of the three catalysts, the *bis*-urea **17** easily outperformed the mixed urea-thiourea compound **16** and the *bis*-thiourea **15**. At lower temperatures, control over the stereocentre-forming event increased using catalysts **7**, **17** and **18** to a maximum of 86% *ee* (entries 11–14).

With enantiocontrol remaining unsatisfactory, we examined the influence of the 1,2-cyclohexanediamine-derived structural unit on catalyst efficacy. This feature is pivotal: catalysts where this group had been altered to either a 5-membered ring-based- (i.e., **18**) or an acyclic analogue (i.e., **19**) promoted either less selective or racemic cycloadditions, respectively (Table 1, entries 14 and 15). Returning to the original motif, employment of the relatively electron-rich amide **14** at −40 °C provided the product in excellent *ee* and d.r. (entry 16). In an attempt to exploit the finding that **17** was clearly superior to **15**, we prepared and evaluated **20**, the urea derivative of **14**. This catalyst did not offer advantages in terms of stereocontrol (entry 17), which indicated that designing catalysts with anion-binding thiourea motifs that incorporate more Lewis-basic iminium ion-binding carbonyl units (see **13a**) may be profitable. Accordingly, replacement of the aromatic amide moiety with an alkyl variant was carried out. To the best of our knowledge, this modification has not been made previously. Gratifyingly, the methyl amide **21** proved a small improvement over **7**

Table 1. Catalyst screening.



Entry	Cat.	Sol.	*T* [°C]	*t* [h]	Conv [%][a]	d.r.[b] (*syn*/*anti*)	*ee* [%][c]
1	**7**	MTBE	RT	2	>98	75:25	32
2	**7**	MeCN	RT	2	>98	60:40	3
3	**7**	THF	RT	2	>98	46:54	17
4	**7**	CH_2Cl_2	RT	2	>98	67:33	32
5	**7**	Et_2O	RT	2	>98	80:20	37
6	**7**	PhMe	RT	2	>98	80:20	50
7[d]	**14**	PhMe	RT	2	>98	80:20	83
8	**15**	PhMe	RT	2	>98	70:30	49
9[d]	**16**	PhMe	RT	2	>98	70:30	60
10	**17**	PhMe	RT	2	>98	77:32	80
11	**7**	PhMe	−30	30	>98	85:15	70
12[d]	**7**	PhMe	−40	30	>98	85:15	75
13	**17**	PhMe	−40	26	>98	82:18	86
14	**18**	PhMe	−40	26	>98	87:13	63
15[d,e]	**19**	PhMe	−40	48	50	50:50	0
16[d]	**14**	PhMe	−40	48	>98	95:5	95
17[d]	**20**	PhMe	−40	30	>98	84:16	75
18[d]	**21**	PhMe	−40	36	>98	86:14	79
19[d,e]	**22**	PhMe	−40	36	>98	93:7	96

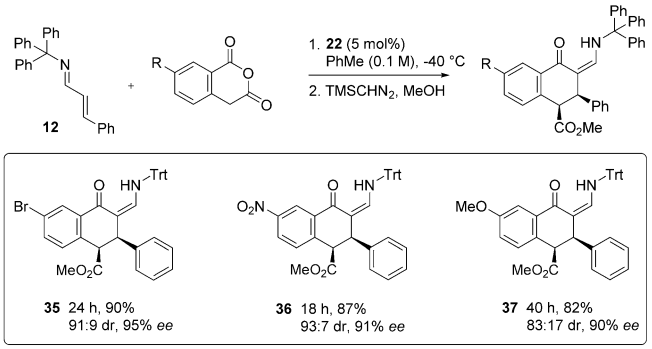
[a] Determined by ^{1}H NMR spectroscopy using *p*-iodoanisole as an internal standard. [b] Diastereomeric ratio (determined by ^{1}H NMR spectroscopy). [c] Determined by CSP-HPLC, see the Supporting Information. [d] Catalyst loading of 5 mol%. [e] Reaction concentration of 0.1 M.

(compare entries 12 and 18), whereas its *tert*-butyl variant **22** (entry 19) was capable of promoting the formation of **13** with 96% *ee* and 93:7 d.r. at just 5 mol% loading and a more convenient concentration of 0.1 M.

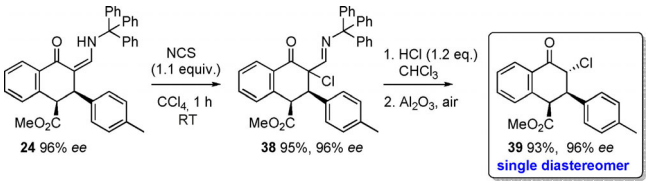
With an enantio- and diastereoselective process in hand, attention turned to the question of substrate scope. It was found that α,β-unsaturated imines bearing electron neutral, electron-deficient, and electron-rich β-aromatic substituents (i.e., leading to tetralones **23**–**29**) reacted with **1** in the presence of **22** (5 mol%) with generally excellent levels of enantio- and diastereocontrol (Table 2). The *p*-CF_3 substituent is a minor exception though **27** could still be formed in 86% *ee* and ca. 3:1 d.r. Tetralones incorporating heterocyclic substituents (i.e., **30** and **31**) could be readily prepared, and β-aliphatic substituents were also eminently compatible (i.e., **32**–**34**).

The homophthalic anhydride component can also be altered. Three substituted homophthalic anhydrides underwent smooth cycloaddition with **12** catalysed by **22** to form **35**–**37** in good-excellent yields, good-excellent diastereocontrol and excellent enantiomeric excess. The anion-stablising bromo- and nitro-substituents facilitated faster, more selective chemistry (Scheme 1).

The synthetic versatility of vinylogous amides is well documented.[15] In an attempt to demonstrate value beyond the usual transformations associated with this functional group, **24** was treated with NCS to produce the α-chloroimine **38**[11a] in excellent yield (Scheme 2). When stirred in a mixture of neutral alumina and chloroform in air, this then underwent a hydrolysis-oxidation-β-ketodecarboxylation cascade in one pot to form the α-chlorotetralone **39** in 96% *ee* as a single diastereomer. To the best of our knowledge, this sequence to α-chloro-1-tetralones is unprecedented and may be of some use given the contemporary challenges associated with developing catalytic asymmetric chlorination methodologies of non-activated ketones.[19]

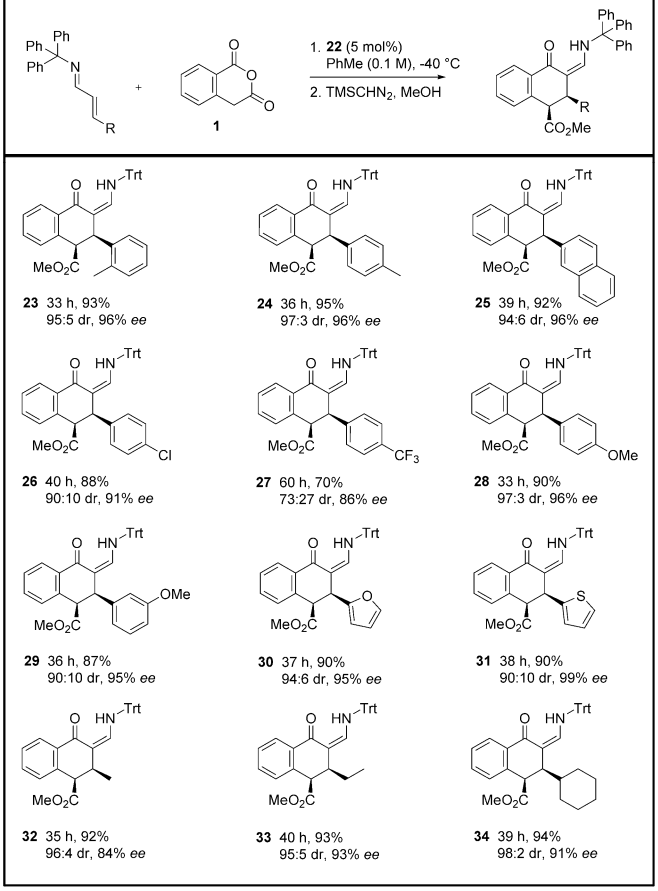


Scheme 1. Substrate scope: anhydride component.



Scheme 2. Conversion of **24** to α-chloroketone **39**.

Table 2. Substrate scope: the imine component.



To provide mechanistic insight into the process, a DFT study (M062X/6–311 + G**// M062X/6-31G*, SMD (toluene), 233 K) was carried out. Preliminary calculations involving the formation of **31** (see the Supporting Information (SI)) indicated that, in the formation of the iminium-enolate ion pair in the presence of **22**, the *s-trans* conformation of the imine is lower in energy than the *s-cis* analogue. The energy profile for the formation of both enantiomers of **31** (Figure 2) is interesting in that, in the case of the generation of the major enantiomer (***R***,***S***)-**31**, the cyclisation step is rate determining, whereas the 1,4-conjugate addition reaction is the slow step leading to the formation of the (*S*,*R*)-antipode. The rate-determining step (RDS) barrier height leading to the major enantiomer is calculated to be lower than the RDS associated with the minor. Both pathways pass through a relatively stable 1,4-conjugate addition adduct and the cyclisation step is essentially irreversible under the reaction conditions. Overall barriers are rather low, which is consistent with smooth cycloaddition at −40 °C.

On examination of TSs associated with the key first stereocentre forming 1,4-conjugate addition reaction step for both major and minor enantiomers, we observed a similar mode of

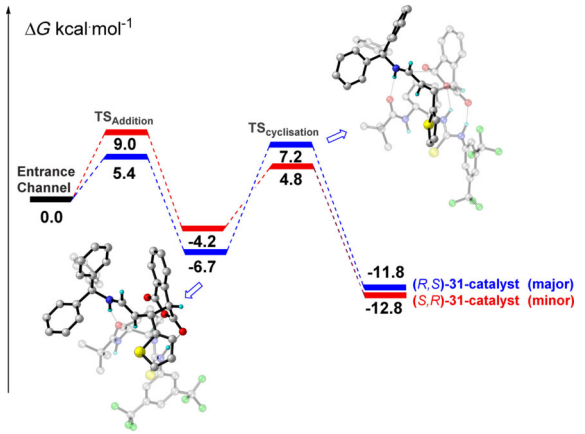


Figure 2. Calculated (DFT) potential energy surface associated with the formation of both enantiomers of **31**.

action to that reported by Seidel and Vetticat during catalysis of the Castagnoli reaction.[9] The catalyst stabilises and organises the encounter between the enolate and iminium ion through hydrogen-bonding interactions—namely between the enolate and the thiourea unit and the iminium ion N–H proton and the catalyst's amide group. In the TS associated with the major enantiomer (***R***,***S***)-**31** (Figure 3, left), the iminium

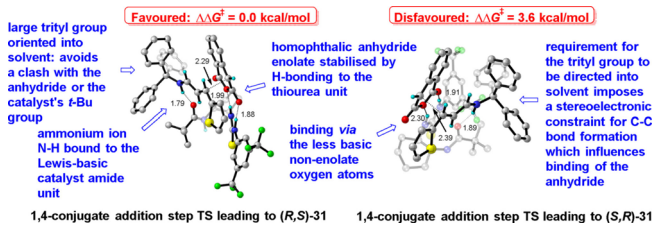


Figure 3. Calculated (DFT) lowest-energy transition-state structures associated with both enantiomers of **31**.

ion is held more tightly (1.79 vs. 1.91 Å) than calculated previously,[9] consistent with the observed improved performance of more basic amide/urea systems in the Tamura reaction under study not observed in the Castagnoli chemistry. The large trityl moiety, which must avoid steric clashes with both the bound enolate and the catalyst's *tert*-butyl group (the exchange of which for a methyl unit led to diminished product *ee*; see catalyst **21**, Table 1) is directed away from the catalyst bulk and into solvent. In the TS leading to the minor (***S***,***R***)-**31** enantiomer (Figure 3, right), in order to accommodate the trityl unit and expose the olefin *re*-face to the nucleophile, the anhydride enolate must be bound through its less basic oxygen atoms to achieve a Bürgi–Dunitz trajectory. This results in weaker hydrogen-bond interactions between both iminium ion/anhydride enolate and the catalyst and a barrier differential ($\Delta\Delta G^{\ddagger} =$ 3.6 kcal mol^{-1}) consistent with the 99% *ee* observed.

In summary, the development of the first highly enantioselective Tamura cycloaddition process of broad scope is reported. The reaction does not require specialised alkenes incorporating electron-withdrawing groups at both olefin termini. Instead, *N*-trityl imine derivatives of simple α,β-unsaturated aldehydes react with homophthalic anhydrides in the presence of a novel catalyst to generate α-tetralones with excellent yield, enantio- and diastereocontrol. Electron-rich, electron-deficient, heterocyclic and aliphatic substituents at the β-position are all well tolerated. The trityl group is of sufficient steric bulk to divert the chemistry away from lactam formation and towards conjugate addition, which also equips the product with a versatile enaminone unit which can be efficiently unmasked as an α-chloro ketone. DFT calculations indicate a bifunctional anion-binding mode of catalyst action and illuminate the distinctive role of the catalyst's amide substituent and substrate trityl group on stereocontrol.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: computational study · cyclic anhydrides · density functional calculations · electrophiles · Tamura cycloaddition

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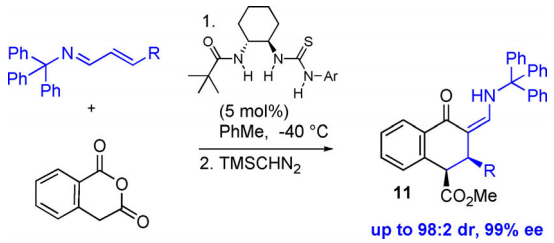
Highly Enantio- and Diastereoselective Catalytic Asymmetric Tamura Cycloaddition Reactions



Tetralone and easy target: A highly enantio- and diastereoselective Tamura cycloaddition process involving simple α,β-unsaturated imines to yield malleable α-tetralones is reported. In addition, DFT calculations provided insight into the catalyst mode of action and the origins of the observed enantiocontrol.