Organocatalysis

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Catalytic Asymmetric Tamura Cycloadditions**

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Abstract: *In the presence of a novel, tert-butyl-substituted squaramide-based catalyst, enolizable anhydrides react with alkylidene oxindoles to generate spirooxindole products of significant synthetic interest with excellent enantio- and diastereocontrol. The methodology is of wide scope and encompasses both homophthalic and glutaconic anhydride derivatives, which lead to structurally diverse products. Glutaconic acid-derived anhydrides undergo a clean post-cyclization decarboxylation process which is not a feature of reactions involving homophthalic acid-derived anhydrides. The unusual influence of reaction temperature on diastereocontrol has been probed, with reactions occurring at 30°C and −30°C delivering products epimeric at one stereocenter only, in near optical purity.*

In 1981 Tamura et al. first reported the reaction of homophthalic anhydride (**1**) with activated alkynes and alkenes at high temperatures (Figure 1 A).[1] These C–C bond-forming processes leading to **2** and **4** have been postulated to proceed by an initial Diels–Alder reaction (via enol **2a**) and subsequent loss of CO_2 from **2b**, although an alternative pathway involving initial Michael-type addition (via enol **2c**) and subsequent ring closure has not been ruled out.[1–3] In the case of alkene substrates, aromatization most likely results by hydride transfer to excess **3**.[2,4] Later it was found that clean deprotonation of the anhydride with stoichiometric strong base allowed the reaction to occur under milder reaction conditions.[5,6] It is noteworthy that these reactions required dienophiles equipped with activating groups at both termini,[7] and a predilection for enol(ate) attack at the most electrophilic dienophile carbon atom was observed.

These reactions have been exploited in the syntheses of medicinally relevant polycyclic aromatic natural products,[8] of which dynemycin A[9] (**5**, Figure 1 B) is a particularly elegant example.

The propensity of the Tamura cycloaddition for stereocenter-ablating aromatization, and the absence of promoters for this reaction have thus far precluded any utility in catalytic asymmetric synthesis. While simple Michael acceptors such as methyl acrylate and acrylonitrile are unreactive substrates, we were intrigued by a report that the enedione **6** underwent reaction with homophthalic anhydride (**1**) without aromatization to give racemic **7** (Figure 1 C).

We have recently[10] shown that the bifunctional organocatalyst **9** can promote the formal cycloaddition of benzaldehyde (**8**) to **1** to afford the substituted dihydroisocoumarin

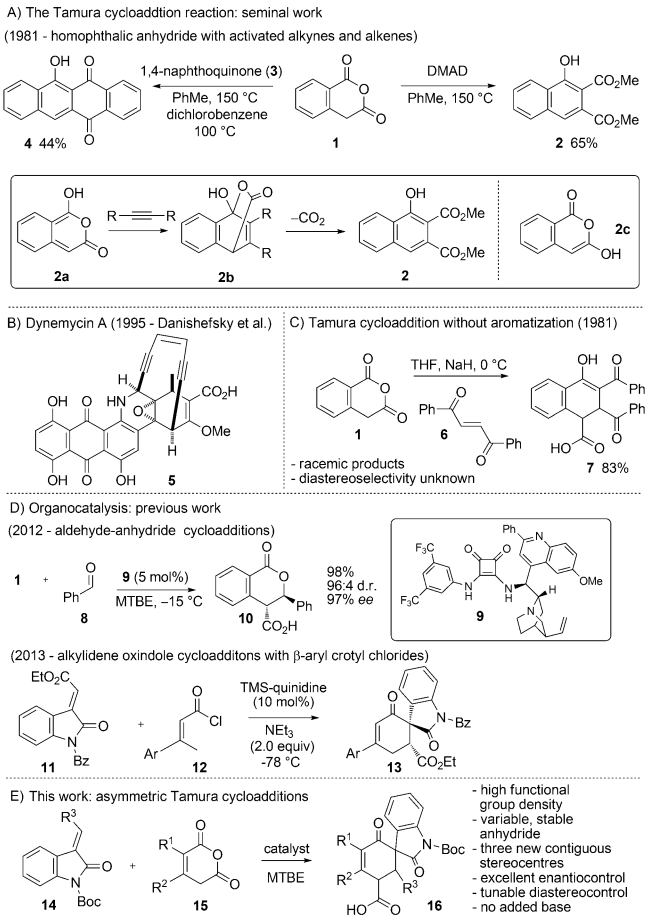

Figure 1. The Tamura cycloaddition reaction. Bz = benzoyl, DMAD = dimethyl acetylenedicarboxylate, MTBE = methyl *tert*-butyl ether, THF = tetrahydrofuran, TMS = trimethylsilyl, Boc = *tert*-butoxycarbonyl.

lactone **10** with excellent yield, and enantio- and diastereocontrol (Figure 1 D).[11] We had posited that **9** both catalyzes the tautomeric equilibrium between **1** and **2c** and organizes the encounter between **2c** and the squaramide-bound **8** by general acid-base catalysis. This offers the possibility of an extension to conjugated electrophiles, and the first enantioselective Tamura cycloaddition reactions. While this manuscript was being prepared, Ye et al.[12] reported the mechanistically distinct TMS-quinidine-catalyzed enantioselective cycloaddition of **11** with β-aryl[13] crotyl chlorides (**12**) at

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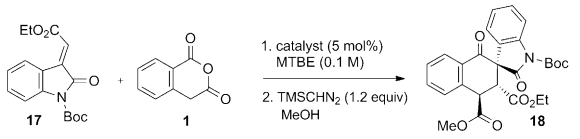
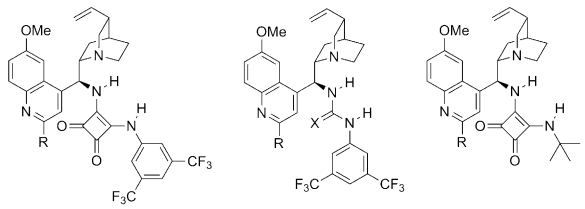
Table 1: Catalyst evaluation and optimization.





9 R = Ph
19 R = H

20 X = S, R = H
21 X = O, R = H
22 X = O, R = Ph

23 R = Ph
24 R = H

Entry	Cat.	*T* [°C]	*t* [h]	Conv. [%][a]	d.r. [%][b]	*ee* [%][c]
1	**9**	30	19	>98	96:3:1	93
2	**19**	30	16	97	97.5:2:0.5	83
3	**20**	30	19	97	98.5:1:0.5	88
4	**21**	30	13	97	98:1:1	88
5	**22**	30	16	>98	98.5:1:0.5	90
6	**23**	30	19	>98	96:3:1	88
7	**24**	30	19	>98	94.5:4:1.5	95
8	**24**	0	17	95	40:59:1	85

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC. Boc = *tert*-butoxycarbonyl.

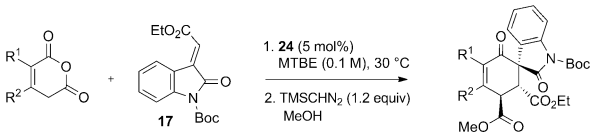
−78 °C in the presence of excess NEt_3 (2.0 equiv, Figure 1 D) to generate the spirooxindoles **13**.

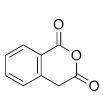
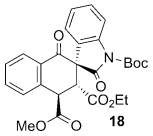
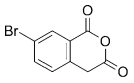
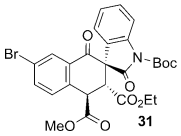
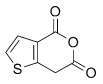
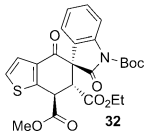
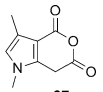
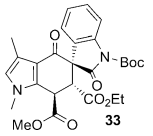
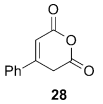
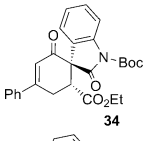
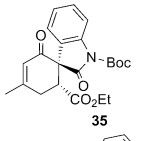
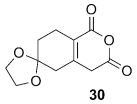
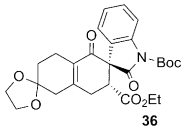
Herein we report catalytic asymmetric Tamura cycloaddition reactions between alkylidene oxindoles **14** and a variety of stable, enolizable anhydrides **15** to afford one-step, base-free access to more densely functionalized 3,3-spirooxindoles (**16**, found in a wide range of bioactive natural products and molecules of medicinal interest),[14] with the formation of two new C–C bonds and three new contiguous stereocenters, all of which are completely carbogenic and one of which is quaternary (Figure 1 E).

In preliminary experiments, the *N*-Boc oxindole **17** was reacted with the stable and the readily handled homophthalic anhydride (**1**) in the presence of squaramide **9** (the previously identified optimum catalyst for the cycloaddition of aldehydes with **1**[10]) in MTBE at 30 °C (entry 1, Table 1).[15a] Under these reaction conditions, the Tamura cycloaddition proceeded to full conversion, thus producing the tetracyclic spiroadduct **18** with excellent diastereo- and enantiocontrol. The use of the corresponding squaramide **19**, which is devoid of the C2′ phenyl moiety, led to improved diastereoselectivity, however product *ee* value decreased significantly (entry 2). The thiourea-based alkaloid **20**[15b–f] proved superior from a diastereocontrol standpoint (entry 3), however enantiocontrol was less efficient than in the reaction catalyzed by **9**. Since neither the corresponding urea **21** nor its C2′-arylated analogue (**22**, entries 4 and 5) were capable of a more enantioselective catalysis than **9**, we returned to catalysts containing the squaramide unit.

The novel *tert*-butyl squaramide catalysts **23** and **24** exhibited interesting behavior: while the C2′-arylated material **23** was inferior to **9** (entry 6, Table 1), the analogue lacking this substituent **24** could catalyze the formation of **18** with excellent diastereocontrol and in 95 % *ee* (entry 7). Intriguingly, a repeat of this reaction at reduced temperature led to a drastic reduction in diastereocontrol and significantly diminished enantioselectivity (entry 8).

Table 2: Substrate scope: Enolizable anhydrides.



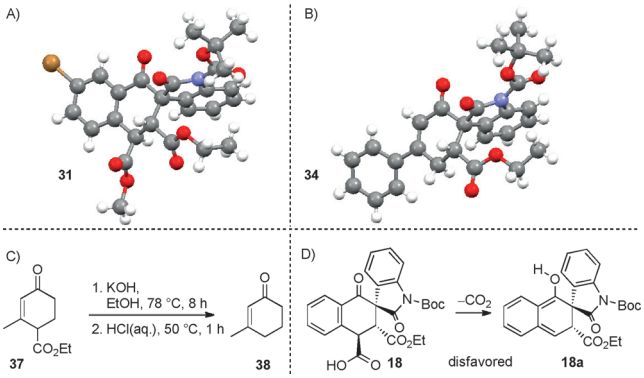
Entry	Anhydride	Product	*t* [h]	Yield [%][a]	*ee* [%][b]
1	 **1**	 **18**	19	92	95
2	 **25**	 **31**	20	95	92
3	 **26**	 **32**	21	96	>99
4	 **27**	 **33**	22	95	95
5	 **28**	 **34**	19	94	99
6	 **29**	 **35**	21	95	>98
7	 **30**	 **36**	26	82	>99

[a] Yield of product isolated after chromatography. [b] Determined by CSP-HPLC.

With a satisfactory catalyst and protocol identified, attention next turned to the question of substrate scope. The Michael acceptor **17** was reacted with a range of enolizable anhydrides **1** and **25–30** in the presence of **24** at 30 °C (Table 2). The tetracyclic diastereomer **18** could be isolated in greater than 90 % yield and 95 % *ee* under these conditions (entry 1). The brominated analogue **31** was formed with comparable efficacy and stereocontrol (entry 2). The cycloaddition of the fused heterocyclic anhydrides **26** and **27** with **17** afforded the corresponding thiophene- **32** and pyrrole-substituted **33** tetracyclic ketones with excellent

enantioselectivity (entries 3 and 4). Gratifyingly, the scope of the methodology is not confined to homophthalic anhydride derivatives: the phenyl glutaconic anhydride (**28**), and its methyl variant **29**, underwent smooth cycloaddition to afford the highly substituted cyclohexenones **34** and **35**, respectively in excellent yields and with near optical purity (entries 5 and 6). These reactions represent the first examples of the expansion of enantioselective cycloadditions involving enolizable anhydrides beyond either homophthalic-[10] or α-aryl succinic[11] analogues. To demonstrate the potential of this protocol for the rapid, efficient, and enantioselective synthesis of complex products, the tricyclic anhydride **30** was reacted with **17** under the influence of **24** to generate **36** in high yield and 99% *ee* (entry 7).

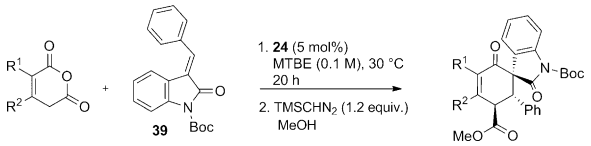
It is noteworthy that **34**–**36** were isolated as cyclohexenones, which are devoid of methyl ester moieties (see the crystal structures of **31** and **34**; Scheme 1 A,B). This transformation, which deletes a stereocenter but renders the product a Michael acceptor primed for further structural elaboration, is most likely the result of a vinylogous ketodecarboxylation and subsequent in situ alkene isomerization, which is reminiscent of the known decarboxylation of Hagemann's ester (itself the parent structure of a family of highly useful synthetic building blocks for natural product synthesis,[16] that is, **37**→**38**, Scheme 1 C) upon hydrolysis. We would suggest that this does not occur in the case of homophthalic anhydride substrates as it would require disturbance of the aromatic system (Scheme 1 D).

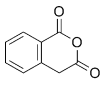
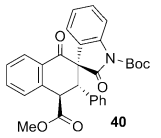
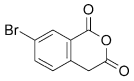
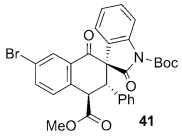
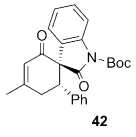


Scheme 1. The crystal structures of **31** (A) and **34** (B), Hagemann's ester (C), and a rationale for the resistance of a homophthalic-anhydride-derived substrate to decarboxylation (D). Gray C, white H, red O, blue N, yellow Br.

Given that previous reports involving the uncatalyzed (racemic) Tamura reaction involve alkenes incorporating activating groups at both termini exclusively, we were interested in evaluating the performance of the less electrophilic benzylidene derivative **39** as a substrate (Table 3). This was found to participate in cycloadditions with the homophthalic anhydrides **1** and **25** to furnish **40** and **41**, respectively in excellent yield (entries 1 and 2). Enantiocontrol, though high (89% *ee*), was marginally diminished relative to the corresponding reactions involving the ester-substituted substrate **17**. In both cases ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated that the products formed with outstanding diastereocontrol. Conversely, the reaction of **39** with the glutaconic anhydride **29** led to the isolation of **42** in reduced yield but with outstanding enantioselectivity (>99%, entry 3).

Table 3: Organocatalytic cycloadditions involving **39**.

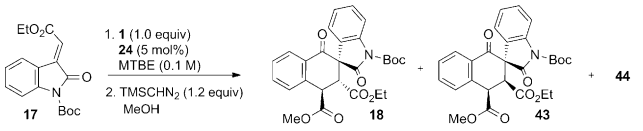


Entry	Anhydride	Product	Yield [%][a]	*ee* [%][b]
1	 1	 40	96	89
2	 25	 41	98	89
3	 29	 42	65	>99

[a] Yield of product isolated after chromatography. [b] Determined by CSP-HPLC.

Finally, we investigated the curious effect of the reaction temperature on both the enantio- and diastereocontrol observed in our preliminary experiments (i.e. entries 7 and 8, Table 1). Upon lowering the reaction temperature (Table 4) from 30 to 20 °C a significant increase in the levels of the kinetic product diastereomer **43** (epimeric at the stereocenter incorporating the ethyl ester) was detected [along with trace levels of another diastereomer **44** of indeterminate configuration], with a concurrent decrease in the *ee* value of **18**

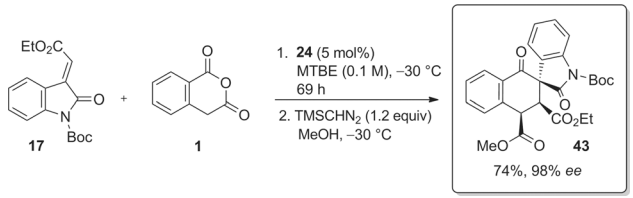
Table 4: The effect of temperature on enantio- and diastereocontrol.



Entry	*T* [°C]	*t* [h]	Conv. [%][a]	d.r. (**18**/**43**/**44**)[b]	**18** *ee* [%][b]	**43** *ee* [%][b]
1[c]	30	19	>98	94.5:4:1.5	95	n.d.
2	20	19	96	90:9.5:0.5	93	n.d.
3[c]	0	17	95	40:59:1	85	n.d.
4	−15	44	>98	34:65:1	95	96
5	−50	18d	85	16:82:2	43	>99
6[d]	−50	15d	91	17:82:1	94	99

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC. [c] Data reproduced from Table 1. [d] Using 20 mol% catalyst loading.

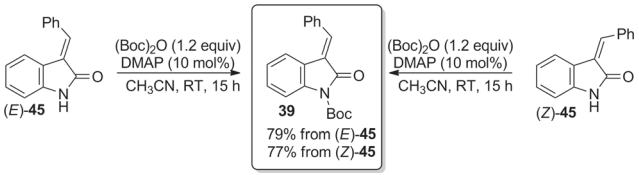
(entries 1 and 2). As the temperature was reduced further, this trend continued. As seen previously, at 0 °C, **43** is formed as the major diastereomer (entry 3), while reactions conducted at progressively lower temperatures favored the formation of **43** in greater amounts and with higher enantiocontrol (at the expense of the *ee* value of **18** and the reaction time; entries 4 and 5). Using a 20 mol % catalyst loading at −50 °C, the cycloaddition proceeded to form **43** as the dominant diastereomer in greater than 99 % *ee* at 91 % conversion (entry 6). Thus selective access to either **18** or **43** is possible simply by changing the reaction temperature. By way of demonstration, the diastereomer **43** can be isolated in 74 % yield and 98 % *ee* from the reaction of **1** with **17** catalyzed by **24** at −30 °C (Scheme 2). This form of highly enantioselective kinetic control significantly augments the potential utility of the methodology in target-oriented synthesis. We observed a similar phenomenon using oxindole **39**, however, in this case the effect was less pronounced.



Scheme 2. Enantioselective synthesis of the *syn* diastereomer of **43** at low temperature.

The stereochemical relationship between **18** and **43** (i.e. epimeric at the ethyl-ester-containing stereocenter only) deserves comment. It is difficult to rationalize this outcome in terms of catalyst–substrate face-selective binding interactions alone, and we were unable to bring about the efficient epimerization of **43** to **18** with amine bases such as diisopropylethylamine. We therefore suggest that **17** may undergo reversible *E* to *Z* isomerization under the reaction conditions. While we could not observe this isomerization by ^{1}H NMR spectroscopic analysis, we did find that during the synthesis of substrate **39**, that DMAP-mediated Boc protection of either pure (*E*)- or (*Z*)-**45** provided (*E*)-**39** exclusively at ambient temperature (Scheme 3). Thus, while a definitive conclusion on this point awaits a full mechanistic study, the involvement of nucleophile-catalyzed isomerization of the alkylidene oxindole starting materials is certainly not impossible.[17,18]

In summary, 32 years after the first report concerning the Tamura cycloaddition reaction, the first catalytic asymmetric variants have been developed. The novel, ad-hoc designed squaramide-based catalyst **24** promotes the highly enantioselective formal cycloaddition of enolizable anhydrides to alkylidene oxindoles to form densely functionalized 3,3-spirooxindole products in excellent yield and stereocontrol. Substitution of the ester functionality on the Michael acceptor for a phenyl ring is well tolerated by the catalyst, and a highly unusual dependence on temperature in relation to diastereocontrol was observed: at higher temperatures the diastereomer **18** could be generated from **1** and **17** with excellent control over the stereochemistry, while at lower temperatures the epimeric diastereomer **43** could be isolated in high yield and in near optical purity. This phenomenon potentially offers the practitioner more precise control over the stereochemical outcome of these reactions than is usually observed in organocatalytic reactions involving alkylidene oxindoles.



Scheme 3. Amine-mediated isomerization of an alkylidene oxindole. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

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Keywords: asymmetric catalysis · cycloaddition · organocatalysis · spirocompounds · synthetic methods

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[2] Y. Tamura, A. Wada, M. Sasho, Y. Kita, *Chem. Pharm. Bull.* **1983**, *31*, 2691.
[3] For a review of formal cycloaddition reactions involving enolizable anhydrides, see: M. González-López, J. T. Shaw, *Chem. Rev.* **2009**, *109*, 164.
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