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Asymmetric Cycloadditions

Asymmetric Organocatalytic Stepwise [2+2] Entry to Tetra-Substituted Heterodimeric and Homochiral Cyclobutanes

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Abstract: An asymmetric synthesis of tetra-substituted cyclobutanes involving an organocatalytic, stepwise [2+2]-cycloaddition is described. The secondary-amine-catalyzed method allows for the hetero-dimerization of two different cinnamic-acid-derived sub-units, opening a novel one-step assembly to densely functionalized, head-to-tail coupled dimeric cyclobutanes in high enantiomeric excess. A series of selective synthetic interconversions in these sensitive cycloadducts is also described.

The synthesis of cyclobutane derivatives has risen in prominence over the last few years in view of an increased recognition of their importance within bioactive natural products, with well over 200 derivatives now known.[1] In addition, cyclobutanes are often used as synthetically useful, strained intermediates. Classical alkylation and photochemical routes to achiral cyclobutanes including solid-state photochemistry[2] have been supplemented[3] with novel methods involving stepwise, thermal [2+2]-cycloaddition reactions mediated by transition metals,[4] organocatalysis,[5] and one-electron oxidants.[6] In addition to expanding the scope of alkene participants, these methods often allow for regio-controlled cycloaddition leading to non-symmetrical dimers and/or asymmetric entries to chiral cyclobutane derivatives.

Although many dimeric and pseudo-dimeric (non-symmetrical) naturally occurring cyclobutanes appear to be derived from the dimerization of cinnamyl, coumaryl, or extended diene amides, the precise enzyme responsible ("[2+2]-ase"),[7a] and hence mechanism of the biological dimerization is unknown. Nonetheless, for non-*meso* examples, such cyclobutanes may be homo-chiral, indicating the involvement of an enzymatic biosynthesis rather than a strictly abiotic photochemical or oxidative dimerization process. In addition, these cinnamic acid derivatives are known to dimerize through either a head-to-head or a head-to-tail alignment leading to regioisomeric cyclobutanes. Examples of head-to-head coupled cyclobutanes include piperarborenine D (Figure 1)[7a] and the iridoid argenteoside A,[7b] whereas head-to-tail derivatives are exemplified by dipiperamide A,[7c] nigramide P,[7d] dipiperamide E,[7e] and argenteoside B,[7b] among many others.[7] The argenteosides have recently been identified as potent inhibitors of heat shock protein 90 (Hsp90), a high-value therapeutic target, whereas dipiperamides A and B have potent activity against cytochrome P450 (CYP) 3A4.

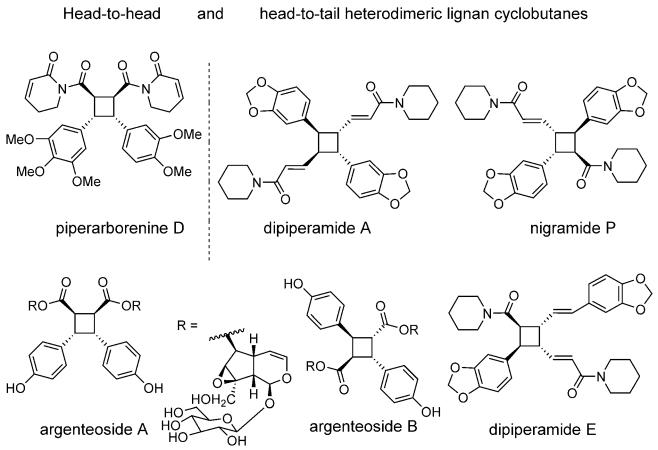

Figure 1. Structures of selected biologically active natural product cyclobutane-containing lignan-dimers including head-to-head (left) and head-to-tail (right) coupled derivatives.

Despite the number of approaches developed to access chiral cyclobutanes,[3] no process has been reported that permits direct asymmetric heterodimerization of two different cinnamyl-derived sub-units. The closest examples reported to date involve remote dienamine-mediated couplings of 3-vinyloxindoles,[5a] nitroolefins,[5c] and vinylpyrroles.[5f] The development of a direct asymmetric heterodimerization process would be of great utility given the valuable biological activities reported for these and other related non-symmetrical dimers, such as sceptrin,[8] and lignans that could be accessed through cyclobutane fragmentation.[2a] In this communication, we report the first examples of organocatalytic heterodimerization of two different cinnamyl-derived olefins in a regioselective and highly enantioselective fashion to yield tetra-substituted cyclobutanes.

A retrosynthetic analysis detailing the potential iminium-ion-mediated cascade to access cyclobutanes is shown in Scheme 1. It was postulated that heterodimerization might be achieved through reaction of a cinnamaldehyde derivative

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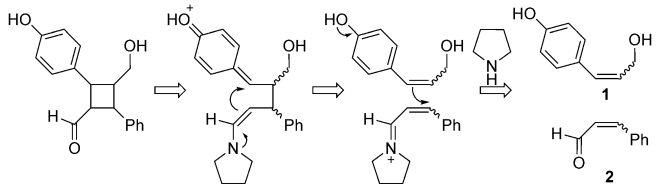
with a cinnamyl alcohol as indicated. Activation of the olefin of cinnamyl alcohol **1** with a 4-hydroxyl group, for example, would direct the stepwise cycloaddition onto the iminium ion derived from **2** in a regioselective fashion. It should be noted that, although organocatalytic Friedel–Crafts reactions of phenols,[9] vinylogous electron-rich anilines,[10] and pyrroles[5f] onto Michael acceptors are known, in no case have two phenylpropanoid sub-units been converted to cyclobutanes through such a method.



Scheme 1. Retrosynthetic analysis of a heterodimeric cyclobutane derivative potentially available from dimerization of a cinnamaldehyde derivative **2** and cinnamyl alcohol **1** precursors.

We began this investigation with attempts to engage isoeugenol **1a** in reaction with cinnamaldehyde **2a** in the presence of the achiral secondary amine pyrrolidine **3a** at room temperature in THF (Table 1, entry 1). We identified that a [2+2]-cycloadduct was being formed slowly, and isolated ***rac*-4a** in 14% yield. A solvent screen (Table 1, entries 1–7) demonstrated a strong preference for polar protic solvents, with methanol being identified as the ideal solvent in a process that provided the cyclobutane ***rac*-4a** as a single diastereomer in 80% isolated yield. We next explored asymmetric induction using L-proline **3b** and several versions of the common diarylsilylprolinol (Jørgensen-type) catalysts (**3c–e**). Interestingly, no product was detected using L-proline (Table 1, entry 8) and only trace amounts of the cyclobutane were detected using the free diphenylprolinol **3c** or the second generation Jørgensen catalyst **3e**, even on extended reaction times (Table 1, entries 9 and 10).

Nonetheless, to our delight, the (*2S*)-diarylsilylprolinol catalyst **3d** proved to be highly efficient, giving the desired product in 77% isolated yield and with 82% *ee* (Table 1, entry 11). The enantioselectivity of the reaction was also significantly improved by cooling to 8 °C (refrigerator) for the duration of the reaction. This process yielded essentially a single enantiomer without any decrease in the isolated yield (Table 1, entry 12). The *ee* of the cyclobutane **4a** was determined using chiral HPLC analysis of the alcohol **5a** in direct comparison to ***rac*-5a** prepared using pyrrolidine as catalyst.

The structure of the isolated cyclobutane **4a** was initially deduced through 1- and 2-D ^{1}H NMR analysis, through which the stereochemistry appeared to be all-*trans*. We hoped to confirm this result as well as to ascertain the absolute stereochemistry of the reaction mediated by secondary amine **3d** through X-ray analysis of a suitable derivative. The reaction of isoeugenol **1a** was repeated using 4-bromocinnamaldehyde, and the resulting cycloadduct **4c** converted to its crystalline semicarbazone **6** (Figure 2). Single-crystal X-ray diffraction analysis confirmed the structure, the crystals proved to be homochiral, and the absolute stereochemistry **6** was defined as shown (Figure 2).

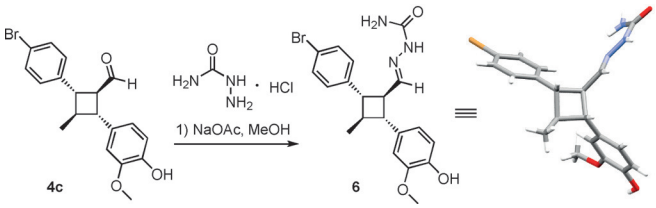
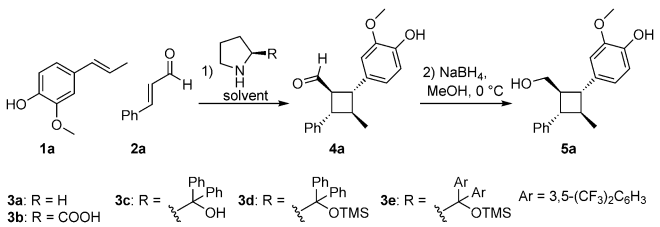


Figure 2. Structure and absolute stereochemistry of the cyclobutane adduct from the [2+2] cycloaddition of 4-bromocinnamaldehyde and isoeugenol as determined via the semicarbazone (CCDC 1456076; see ref. [14]).

While optimizing the conditions for the asymmetric catalysis, we discovered that the [2+2] cycloaddition is in fact thermally reversible and subject to an interesting dynamic kinetic resolution. When purified racemic **4a** was stirred with catalyst **3d** in methanol at room temperature for several days, partial reformation of starting materials was noted. Re-isolation and analysis of **4a** showed enantioenrichment of the product in favor of the opposite enantiomer **ent-4a** (23% *ee*), produced using catalyst **3d**. This result is readily explained by the process of mi-

Table 1. Catalyst and solvent screening for the organocatalytic [2+2] cycloaddition[a]



Entry	Catalyst (*x* mol%)	Solvent	Time	Yield[b] [%]	*ee*[c] [%]
1	**3a** (20)	THF	48 h	14	–
2	**3a** (20)	DMSO	48 h	26	–
3	**3a** (20)	CH_2Cl_2	48 h	30	–
4	**3a** (20)	Toluene	48 h	31	–
5	**3a** (20)	*i*PrOH	48 h	46	–
6	**3a** (20)	EtOH	48 h	53	–
7	**3a** (20)	MeOH	48 h	80	–
8	**3b** (20)	MeOH	48 h	n.r.	–
9	**3c** (10)	MeOH	4 d	Trace	n.d.
10	**3e** (10)	MeOH	4 d	Trace	n.d.
11	**3d** (10)	MeOH	5 d	77	82
12[d]	**3d** (10)	MeOH	5 d	78	97

[a] Unless otherwise noted, reactions were performed with **1a** (0.66 mmol), **2a** (1.00 mmol), and catalyst in 1.33 mL of solvent. Reactions using catalysts **3b–e** were performed on half scale. [b] Isolated yield of the cyclobutane aldehyde; n.r. = no reaction. [c] Enantiomeric excess (*ee*) was determined on the reduced cyclobutanol employing chiral HPLC analysis; n.d. = not determined. [d] Reaction performed at 8 °C without stirring.

croscopic reversibility, with catalyst **3d** favoring the lower energy retro-cycloaddition pathway available. The cycloaddition is therefore forward-driven under kinetic conditions by enthalpic considerations (formation of two sigma bonds) but reversible thermodynamically at higher temperatures. The cyclobutane aldehyde **4a** can readily be isolated and handled under normal conditions, but should be prevented from re-establishing an iminium ion mediated cycloreversion.

The scope of the reaction was next investigated using isoeugenol **1a** in reaction with a variety of aromatic α,β-unsaturated aldehydes **2** (Table 2A). The desired alkenals were readily prepared using our recently described two-carbon homologation reagent.[11] To avoid cycloreversion, the aldehydes were immediately reduced after the cycloaddition reaction was complete. The cyclobutane adducts were obtained in good yields (66–80%) and very high *ee* values (91–98%) with either electron-donating or electron withdrawing substituents on the alkenal **2**, which was also successful with *ortho*, *meta*, or *para* substituents.

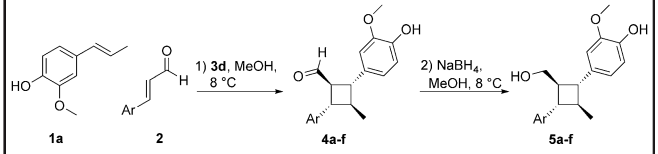
We next explored the reaction of cinnamaldehyde **2a** with several different electron rich alkenes to probe the donor requirements of the reaction (Table 2B). Whereas isoeugenol **1a** was used successfully in many examples, its corresponding methyl ether methylisoeugenol **1b** did not produce a cycloadduct, demonstrating that a free phenol is required for the donor to enter into the organocatalytic [2+2] cascade. Most importantly, in view of access to the natural cinnamyl-derived cyclobutanes, the reaction of cinnamaldehyde proved highly successful with coniferyl alcohol **1c**, giving rise to the cyclobutane **4g** in 77% isolated yield as essentially a single enantiomer. Hence, the method allows for the catalytic asymmetric head-to-tail dimerization of a cinnamaldehyde derivative with a cinnamyl alcohol permitting access to heterodimeric cyclobutane carboxaldehydes (vide infra). The reaction was also successful employing (*E*)-1-(4′-hydroxyphenyl)-1-butene **1d**, yielding the corresponding cycloadduct **5h** (after reduction). Overall, the results show that a conjugated free-phenolic substituent is required to activate the electron-rich donor olefin for successful engagement in the reaction, and that the reaction works well with a wide variety of cinnamaldehyde derivatives **2**.

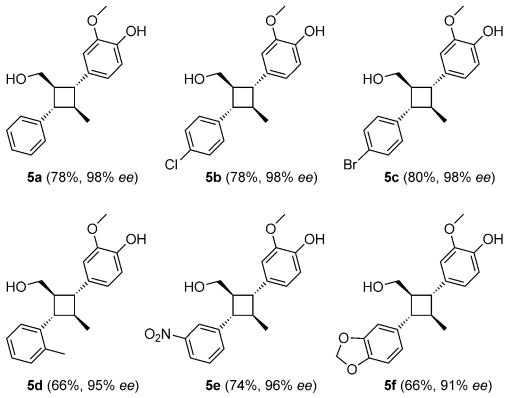
A selection of transformations were developed to investigate applications while retaining chirality on the heterodimeric cyclobutane **4g** (Scheme 2). Direct reduction of **4g** would lead to a *meso*-triol (not shown), however **4g** could be converted to the *bis*-benzoate **7**, allowing reduction of the aldehyde to yield the cyclobutamethanol **8**. Chiral HPLC analysis of **8** demonstrated that homochirality was maintained through this tightrope of reactions (Scheme 2, ii and iii).

In addition, ***rac*-4a** was readily converted to the diacetate **9**, reduction of which led quickly to the diacetoxy alcohol **10**. We also discovered that reaction of **9** or **10** with excess sodium borohydride led to the reductive cleavage of the *ortho*-methoxy acetate, most likely through a chelation-assisted pathway. This reaction yields the free phenol derivative **11**, an intermediate that appears suitable for one-electron oxidative fragmentation reactions.[2a] Finally, reaction of ***rac*-4g** with the ylide derived from (ethoxycarbonylmethyl)triisobutylphosphonium bromide, gave the two-carbon extended ester **12**, analogous to natural products such as nigramide P (Figure 1).

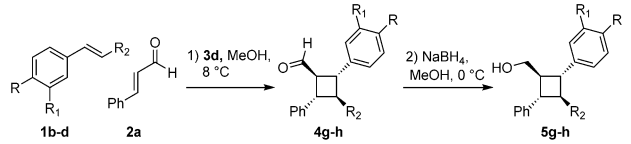
Table 2. Scope and selectivity of the organocatalytic [2+2] cycloaddition reaction (isolated yield, *ee*).

A) Reaction of **1a** with acceptor α,β-unsaturated aldehydes.

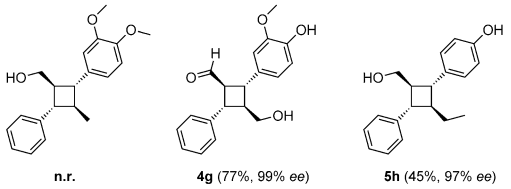




B) Reaction of cinnamaldehyde with other donor alkenes.



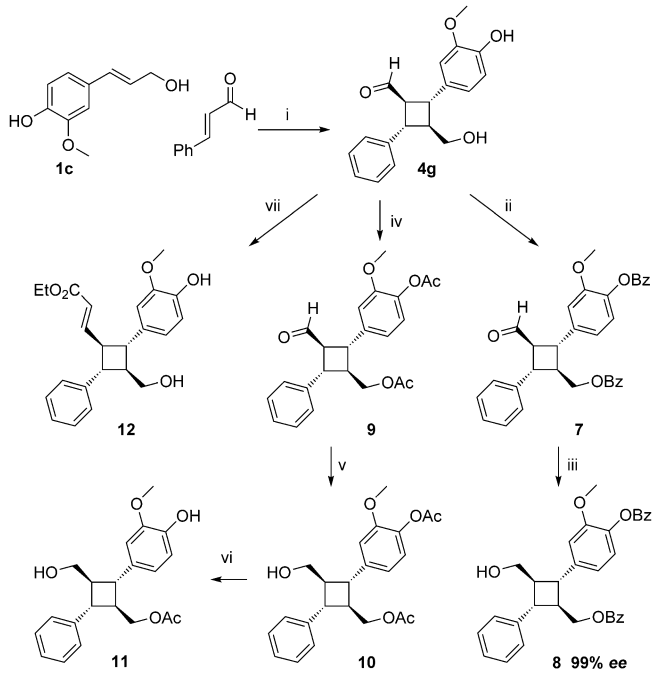
1b: R = R_1 = OMe, R_2 = Me **1c**: R = OH, R_1 = OMe, R_2 = CH_2OH **1d**: R = OH, R_1 = H, R_2 = CH_2CH_3



Unless otherwise noted, reactions were performed with **1** (0.33 mmol), **2** (0.50 mmol), and catalyst **3d** (0.1 equiv) in 0.66 mL of MeOH, over 5 days at 8 °C. Yields of the cyclobutane aldehyde are reported; *ee* was determined by HPLC analysis of the reduced cyclobutanes; **4g** was benzoylated prior to reduction to avoid production of a meso diol; n.r = no reaction.

It is important to note that the two-step sequence of i followed by vii (Scheme 2) opens a controlled access to vinyl-cyclobutanes, avoiding possible [4+2]-type adducts[7d] that often co-occur with the natural cyclobutanes.

From a mechanistic perspective, we were able to successfully conduct the stepwise [2+2]-reaction of **1a** with **2a** using pyrrolidine **3a** catalysis either in the dark or in the presence of 5 mol% 4-tertbutylcatechol indicating that neither photochemical nor oxidative processes are involved. In conjunction with the very high *ee* values observed, the evidence indicates that



Scheme 2. Selective manipulations of **4 g**. i: **3 d**, MeOH, 8 °C, 5d (0.1 equiv), 77 %. ii: Benzoyl chloride (2.2 equiv), 4-dimethylaminopyridine (0.1 equiv), diisopropylethylamine, CH_2Cl_2, 58 %. iii: $NaBH_4$ (1.0 equiv), EtOH, 95 %. iv: acetyl chloride (2.2 equiv), 4-dimethylaminopyridine (0.1 equiv), diisopropylethylamine, CH_2Cl_2, 50 %. v: $NaBH_4$ (1.0 equiv), MeOH, 20 min, 90 %. vi: $NaBH_4$ (5 equiv), MeOH, 8 h (90 %). vii: (ethoxycarbonylmethyl)triisobutylphosphonium bromide (3.0 eq), KO*t*Bu (3.0 eq), THF, 0 °C–rt, 1 h, 75 %.

the reaction proceeds through a stepwise formal [2+2] using tandem iminium-enamine catalysis (Figure 3).

The stereochemistry of the reaction is rationalized through the transition-state assembly depicted in Figure 4 using catalyst **3 d**. The donor substituent (most likely the phenoxide anion) attacks the least hindered *Si*-face of the iminium ion (Figure 4, (**I**)) with the diarylprolinol substituent placed distal

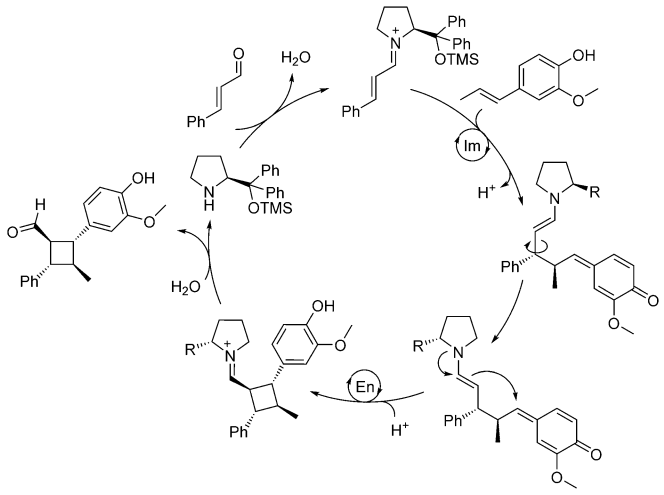


Figure 3. Proposed catalytic cycle and absolute stereochemical configuration of cyclobutane derivatives.

allowing an overall *anti*-periplanar HOMO–LUMO alignment for the first step of the cascade. The model shows that a strong possibility exists for stabilizing face or edge-on π–π secondary orbital interactions in this assembly. The enamine (**II**) now closes the cyclobutane ring by adding on to the *p*-quinomethide intermediate, with iminium hydrolysis completing the cascade.

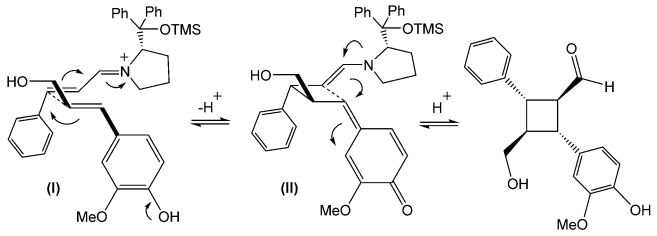


Figure 4. Transition-state assembly using catalyst **3 d** leading to the product of absolute stereochemistry shown in Figure 3

In conclusion, we report the discovery of novel organocatalytic methodology for the asymmetric synthesis of highly functionalized chiral cyclobutanes in a regiospecific manner from α,β-unsaturated aldehydes and alkenylphenols. The process yields heterodimeric head-to-tail coupled cyclobutanes in good yield and with excellent enantioselectivity.

A selection of transformations on the cyclobutane carboxaldehyde **4 g** have been developed to showcase the potential of this method to access chiral synthetic intermediates and adducts suitable for fragmentation reactions or conversion to natural product-containing cyclobutanes and analogs. Finally, the ease with which these strained tetrasubstituted cyclobutanes are formed under iminium-ion catalysis opens another consideration regarding the nature of the [2+2]-ase,[7a] which could lead to such natural products under non-oxidative and non-photoinduced conditions. As novel methods for the synthesis of cyclobutanes are actively sought,[3] the present discovery highlights a widening gap in comparison to classic approaches to "tetramethylene" carboxylates[12] and cyclobutane itself,[13] in terms of reaction yield, regio-control, and now one-step asymmetric entry to these intermediates. Our group is actively exploring umpoled variations of the chemistry to access head-to-head dimers as well as applications in total synthesis.

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Keywords: asymmetric synthesis · cyclobutanes · lignan dimers · organocatalysis

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[14] CCDC 1456076 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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