COMMUNICATION

A Brønsted acid catalyzed tandem reaction for the diastereoselective synthesis of cyclobuta-fused tetrahydroquinoline carboxylic esters

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A novel Brønsted acid catalyzed tandem reaction provides highly functionalized cyclobuta-fused tetrahydroquinoline carboxylic esters from anilines and 2-alkylenecyclobutanones and in good to high yield. During the reaction a diastereoselective dynamic kinetic resolution is achieved, resulting in the formation of three contiguous stereocenters with high stereoselectivity.

Cyclobutanones play a key role as intermediates in organic synthesis due to their inherent ring strain and versatile transformability.[1] They can be converted easily into a wide panel of synthetically valuable compounds via ring-expansion, ring-contraction or ring-opening reactions. In particular, 2-alkylenecyclobutanones have received increasing attention recently (Fig. 1). Yu *et al* reported the Baeyer-Villiger oxidation reaction of 2-alkylenecyclobutanones,[2] while Song *et al* developed the palladium-catalyzed 1,2-addition of boronic acids followed by ring opening to afford γ,δ-unsaturated ketones.[3] The Wu & Xia groups discovered a silver-catalyzed synthesis of 3-(pyrazolo-[5,1-*a*]isoquinolin-1-yl)propanoic acids from 2-alkylenecyclobutanones and *N*'-(2-alkynylbenzylidene) hydrazides,[4] as well as the palladium-catalyzed reaction of 2-(2-bromobenzylidene)cyclobutanone with 2-alkynylphenols to provide benzo[*b*]naphtho[2,3-*d*]-oxocin-6-ones.[5] It is of note that in each of these applications the four-membered ring is transformed into some other structural fragment.

Tetrahydroquinolines are a very important class of nitrogen heterocycles with numerous biological activities[6] and for which various synthetic methodologies have been established.[7] However, only two isolated syntheses of a cyclobuta-fused tetrahydroquinoline have been described (Fig. 1). The first was the Lewis acid induced cycloaddition of an *N*-methylene aniline equivalent to 1,2-bis(trimethylsilyloxy)cyclo-butane,[8] while the second implicated the tandem Brønsted acid catalyzed ring-enlargement-annulation reaction of a cyclopropylcarbinol that required an electron-rich aromatic ring.[9]

In continuation of our studies of reactive small-ring carbocyclic systems,[10] we considered that the Brønsted acid catalyzed aza-Michael addition of an aryl amine to a 2-(carboxymethylidene) cyclobutanone followed by an intramolecular aza-Friedel-Crafts cyclization[11] might provide a rapid access to a new series of functionalized cyclobuta-fused tetrahydroquinoline carboxylic esters (Fig. 1). This would constitute an original synthetic application of 2-alkylenecyclobutanones in which the 4-membered ring is preserved, to provide new cyclobuta-fused tetrahydroquinolines which are unusual conformationally-restricted α-amino acid derivatives. Herein, we describe the successful development of this methodology.

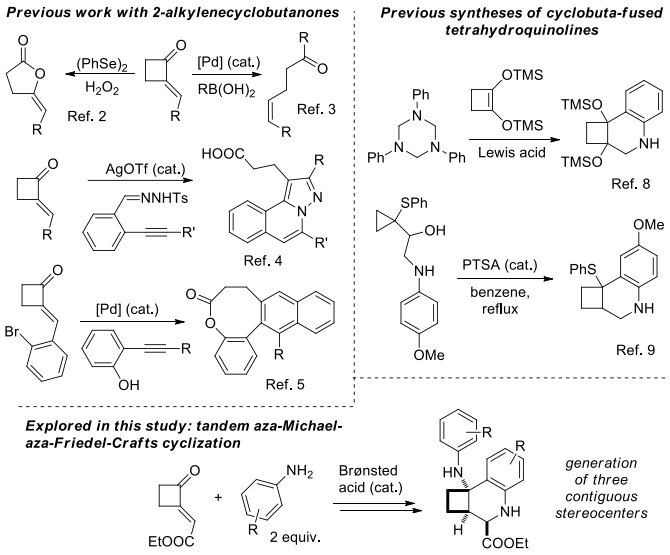


Figure 1. Previous studies and the outline of the present objective.

2-Alkylenecyclobutanone (*E*)-**1a** was selected as the representative substrate to begin our studies.[12] The room temperature reaction between (*E*)-**1a** and aniline **2a** (2 equiv.) was monitored using ^{1}H NMR spectroscopy in order to find the optimal reaction conditions (Table 1). In a first experiment in dichloromethane (entry 1) the reaction did not proceed, while in neat conditions (entry 2) the substrate was transformed entirely but gave principally the intermediate **4a/4a'** with negligible diastereoselectivity (d.r. 52:48). Returning to solution state experiments, the presence of a Brønsted acid additive (10 mol%) had little beneficial effect (entries 3-6), until PTSA emerged as a singularly efficient catalyst for the complete conversion of the substrates into the target cyclobuta-fused tetrahydroquinoline **3a/3a'** with good diastereoselectivity

(entry 7). We were pleased to find that PTSA retained its efficiency in several other solvents (entries 8-11), facilitating complete conversion into **3a/3a'** with diastereoselectivity which reached 85:15 in both THF and toluene (entries 10 and 11). The isolated yield from the reaction in toluene (entry 11) was 83%, and we retained these conditions as standard for the next part of the study.

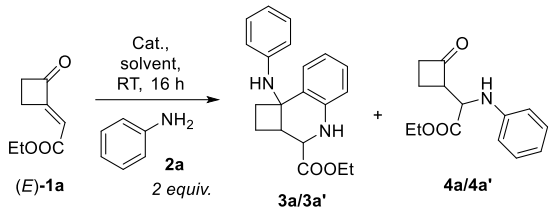
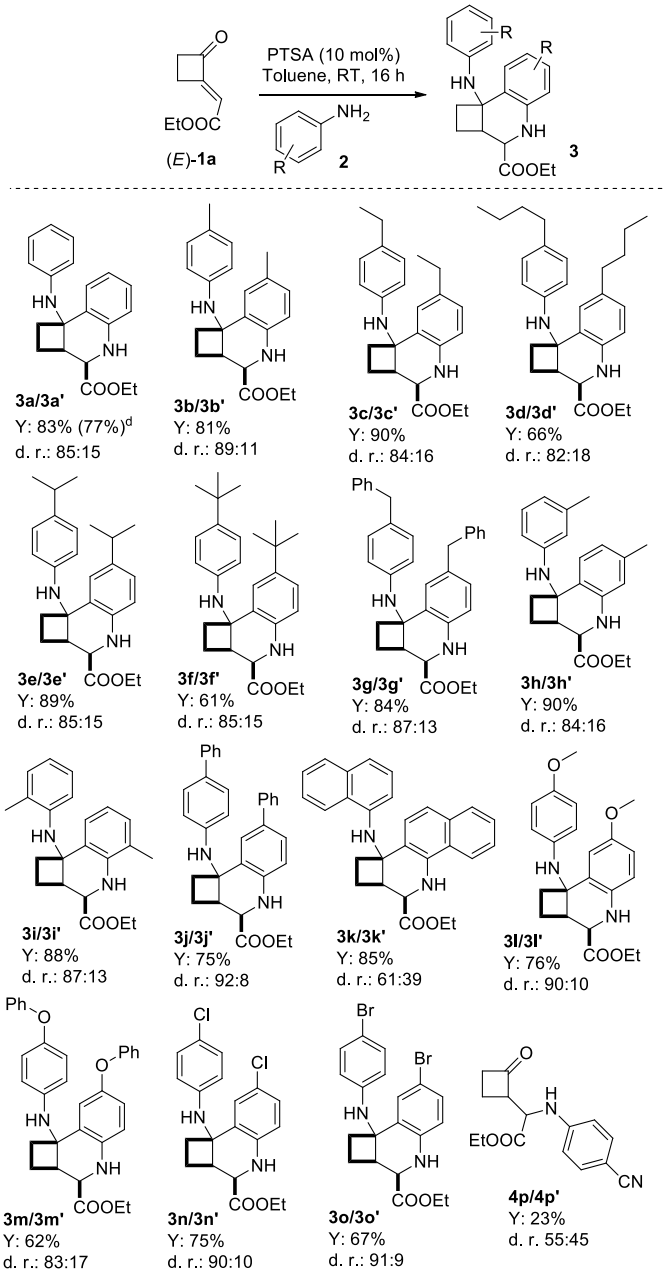


Table 1 Screening of the reaction conditions[a]

Entry	Solvent	Cat. (10 mol%)	Ratio **3a/3a' : 4a/4a'**[b]	**3a/3a'** d. r. (%)[b]
1	CH_2Cl_2	-	-	-
2	-	-	29 : 71	76:26
3	CH_2Cl_2	MsOH	44 : 56	87:13
4	CH_2Cl_2	CH_3COOH	18 : 82	81:19
5	CH_2Cl_2	PhCOOH	20 : 80	82:18
6	CH_2Cl_2	BNDHP[c]	23 : 77	81:19
7	CH_2Cl_2	PTSA	> 99 : 1	79:21
8	CH_3COOEt	PTSA	> 99 : 1	83:17
9	CH_3CN	PTSA	> 99 : 1	71:29
10	THF	PTSA	> 99 : 1	85:15
11	Toluene	PTSA	> 99 : 1 (83)[d]	85:15

[a]Reaction conditions: (*E*)-**1a** (0.26 mmol), **2a** (0.52 mmol), catalyst (0.026 mmol), solvent (0.5 mL). [b]Determined by ^{1}H NMR. [c]BNDHP = 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate. [d]Isolated yield.

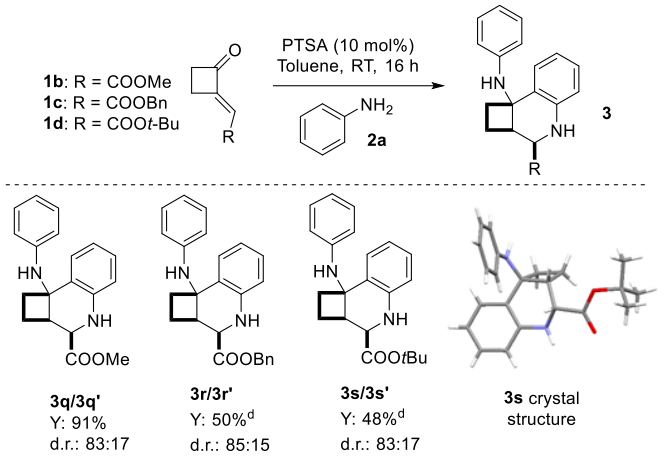
The scope of the reaction was evaluated using a panel of substituted anilines **2b-p** and (*E*)-**1a** in toluene. Results are presented in Scheme 1. Anilines **2b-d** bearing linear alkyl groups (Me, Et, *n*-Bu) at the *para* position furnished the corresponding tetrahydroquinolines **3b**-**d** in good to high yields (66-90%) and diastereoselectivities better than 4:1. The reaction also worked well with anilines **2e-g** bearing more sterically-challenging groups (*i*-Pr, *t*-Bu, Bn) at the *para* position providing derivatives **3e**-**g** in 61-84% yields and with diastereoselectivities better than 5:1. *m*-Methylaniline **2h** gave a high yield (90%) of tetrahydroquinoline **3h** as a single regioisomer and with good diastereoselectivity (d.r. 84:16), while *o*-methylaniline **2i** provided the corresponding product **3i** in similarly high yield (88%) and diastereoselectivity (d.r. 87:13) *p*-Phenyl aniline **2j** and α-naphthylamine **2k** were also examined and the tetrahydroquinolines **3j**-**k** were again isolated in good to high yields (75-85%) and with moderate to high diastereoselectivities (d.r. 61:39-92:8). Anilines **2l**-**o**, bearing oxy- and halo- substitutents (MeO, PhO, Cl, Br) at the *para* position, were accommodated without difficulty and afforded the products **3l**-**o** in 62-76% yields and high diastereoselectivities (d.r. 83:17-91:9). The strongly deactivated *p*-cyanoaniline **2p** yielded only the intermediate **4p/4p'** in low yield (23%) and with poor diastereoselectivity (d.r. 55:45).



[a]Reaction conditions: (*E*)-**1a** (0.26 mmol), **2** (0.52 mmol), PTSA (0.026 mmol), toluene (0.5 mL). [b]Isolated yield. [c]Diastereoisomeric ratio was determined by ^{1}H NMR. The major diastereoisomer is illustrated; see text for details. [d]Performed using 4.3 mmol of (*E*)-**1a**.

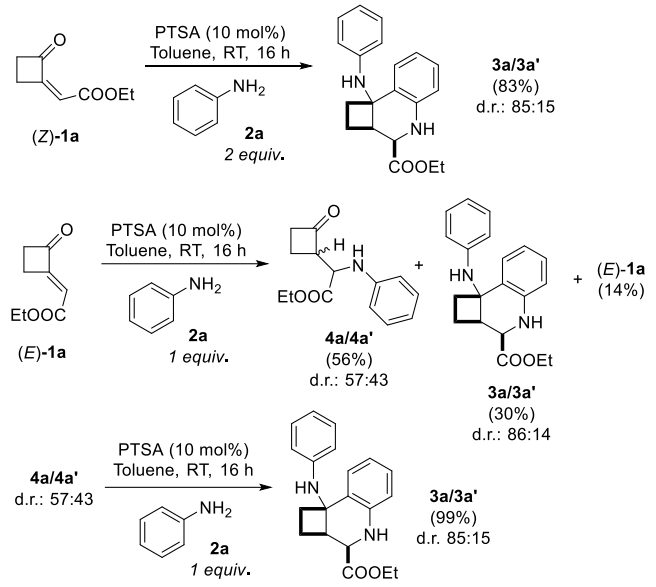
Scheme 1 Substrate scope of the reaction using substituted anilines.[a,b,c]

Bearing in mind that products **3** are protected α-amino acid derivatives, the reaction protocol was tested using aniline **2a** and other ester-functionalized 2-alkylenecyclobutanones, as shown in Scheme 4. The methyl ester derivative (*E*)-**1b** performed just as well as its ethyl ester homologue and delivered the anticipated product **3q/3q'** in high yield (91%) and diastereoselectivity (d.r. 83:17). With the benzyl and *t*-butyl esters (*E*)-**1c** and (*E*)-**1d**, heating (70 °C) was required in order to obtain the target cyclobuta-fused tetrahydroquinolines **3r/3r'**and **3s/3s'**, in somewhat lower yield (48-50%) but with sustained high diastereoselectivity (d.r. 83:17-85:15).



[a]Reaction conditions: **1** (0.26 mmol), **2a** (0.52 mmol), PTSA (0.026 mmol), toluene (0.5 mL). [b]Isolated yield. [c]Diastereoisomeric ratio was determined by ^{1}H NMR. The major diastereoisomer is illustrated; see text for details. [d]Reactions were performed at 70 °C.

Scheme 2 Exploration of the substrate scope of cyclobutanones.[a, b, c, d]

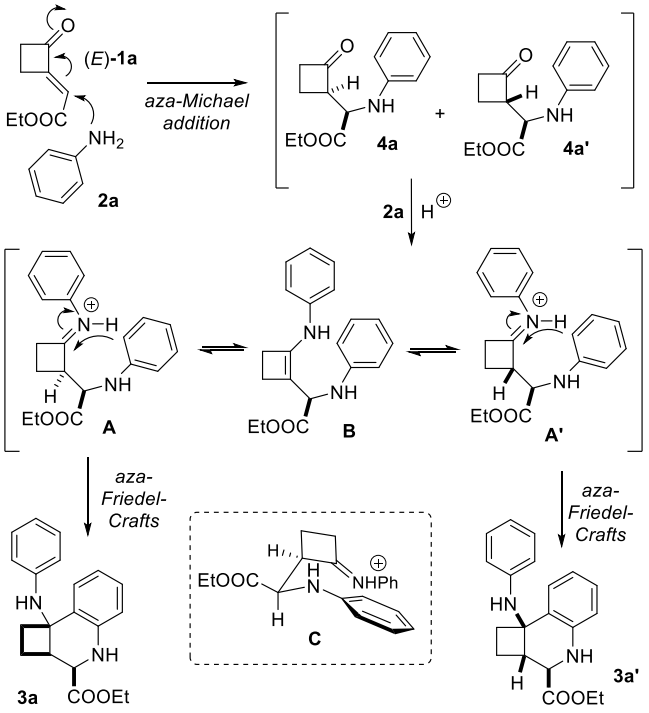


Scheme 3 Control experiments.

In order to ascertain the relative configuration of the three newly-formed stereocenters of adducts **3**, we performed an X-ray diffraction analysis on compound **3s**, obtained as crystalline solid after separation from its minor diastereoisomer **3s'** by silica gel column chromatography. As illustrated in Scheme 2, compound **3s** has the expected *cis*-[4,6] ring junction, while the ester group on the 6-membered ring is *cis* with respect to the fused cyclobutane ring. The same *cis,cis* geometry was assigned to each of the major diastereoisomers of **3** obtained in this work, on the basis of the highly uniform ^{1}H NMR vicinal coupling constant between the α-amino acid proton and the ring junction proton (in the range 3.6-3.9 Hz) observed over the entire series of 18 compounds. [13]

To obtain insight into the stereochemical issues at play, we conducted the control experiments outlined in Scheme 3. Significantly, when the standard one-pot conditions were applied to (*Z*)-**1a** the result was essentially the *same* as that with (*E*)-**1a** as the substrate, *i.e.* **3a/3a'** was obtained with d.r. 85:15. Treatment of (*E*)-**1a** with one equivalent of **2a** in the standard conditions gave a mixture of cyclobutanonone **4a/4a'** (56%, d.r. 57:43), cyclobuta-fused tetrahydroquinoline **3a/3a'** (30%, d.r. 86:14) and unreacted starting material (14%). It was noteworthy that the diastereoselectivity in the formation of **4a/4a'** was poor, as had been the case for **4p/4p'** (see above). The 57:43 cyclobutanonone mixture **4a/4a'** was subsequently treated with one equivalent of **2a** in the standard conditions, resulting in its complete conversion into **3a/3a'** (d.r. 85:15).

These observations suggest that the stereochemical configuration of compound **3** obtained via the tandem procedure is determined in the final step and is independent of the configurations of the starting material **1** and the intermediate **4**.

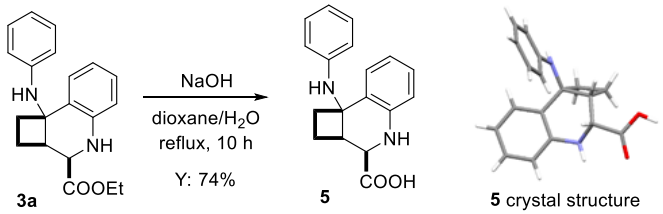


Scheme 4 Plausible mechanism for the tandem reaction (illustrated for (*E*)-**1a** and **2a**) and the origin of the diastereoselectivity.

On the basis of the above observations, a mechanistic analysis of the tandem reaction can be proposed, as shown in Scheme 4. In the first step, the aza-Michael addition of aniline **2** to 2-alkylenecyclobutanone **1** gives a mixture of diastereoisomeric cyclobutanones **4** and **4'** with little selectivity. Each of these

compounds reacts with a second equivalent of aniline **2** to form iminium intermediates **A** and **A'**, which may undergo an intramolecular aza-Friedel-Crafts cyclization to give cyclobuta-fused tetrahydroisoquinolines **3a** and **3a'**, respectively. Since the acid catalyzed equilibration of **A** and **A'** via enamine **B** is likely to be fast relative to cyclization step, a dynamic kinetic resolution[14] appears to be operating at the annulation step. A possible explanation for this selectivity may be that **A** can adopt a conformer **C**, propitious for cyclization, in which the ester group is in a pseudo-equatorial position.

Finally, we verified that compound **3a** could be converted into the corresponding cyclobuta-fused tetrahydroquinoline carboxylic acid **5**. This was achieved readily by treatment with sodium hydroxide without epimerization at the α-amino acid centre (Scheme 5). Compound **5** was obtained in good yield as a single diastereoisomer, with an unchanged diagnostic vicinal coupling constant of 3.7 Hz. It's *cis,cis* geometry was confirmed by an X-ray diffraction analysis (Scheme 5).



Scheme 5 Synthesis of tetrahydroquinoline carboxylic acid **5**.

Conclusions

In summary, we have established a Brønsted acid catalyzed synthesis of diversely substituted cyclobuta-fused tetrahydroquinoline carboxylic esters through a new tandem aza-Michael addition-aza-Friedel-Crafts cyclization process, throughout which the usually-reactive cyclobutane ring remains intact. The sterically hindered α-amino acid derivatives are obtained with diverse substitution profiles and generally high diastereoselectivities. The novel catalytic system established here would appear amenable to further development and applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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most plausible geometry for the minor diastereoisomer series **3'** is a *cis*-[4,6] ring junction and the ester group *trans* to the fused cyclobutane ring.

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