Communications

Cycloaddition



F. de Nanteuil, J. Waser* ___ **IIII**-**IIII**

Synthesis of Aminocyclobutanes by Iron-Catalyzed [2+2] Cycloaddition



Fab Four: An iron-catalyzed [2+2] cycloaddition furnishes aminocyclobutanes with a broad range of substituents in excellent yields and diastereoselectivities. The products can be obtained on a gram scale and can be further converted to β peptide derivatives in a few steps. Furthermore, a [4+2] cycloaddition between an aminocyclobutane and an olefin leads to the corresponding cyclohexylamines.

Cycloaddition

Synthesis of Aminocyclobutanes by Iron-Catalyzed [2+2] Cycloaddition**

Florian de Nanteuil and Jérôme Waser*

Locking the spatial orientation of the substituents of a molecule is essential in order to induce desirable properties such as bioactivity or supramolecular organization. Nitrogensubstituted cyclobutanes in particular combine a small and rigid carbocyclic skeleton with amine-based functional groups, which are omnipresent in bioactive compounds.^[1] In fact, this scaffold can be found in natural or synthetic biologically active compounds such as lannotinidine F (1), cyclobut-G (2), or rhodopeptine analogue 3 (Figure 1).^[2] The



Figure 1. Examples of aminocyclobutanes in natural products and synthetic bioactive compounds.

use of aminocyclobutanes as constrained amino acids has also been studied, as their introduction into peptides results in foldamers with interesting properties ranging from cellpenetrating agents to low-molecular-weight gelators.^[3]

In addition to their exceptional structural properties, cyclobutanes are also versatile synthetic precursors.^[4] Nevertheless, the use of donor–acceptor-substituted cyclobutanes to access formal 1,4-dipoles is far less exploited than the use of cyclopropanes to access formal 1,3-dipoles.^[5] The first example of such a process was reported by Saigo and co-workers in 1991, who described a formal [4+2] cycloaddition between aminocyclobutanes and carbonyl compounds.^[5a] However, the nitrogen atom was lost during the process. In subsequent related studies, carbo- and alkoxy-substituted four-membered rings were employed.^[5b-f]

The structural and synthetic versatility of aminocyclobutanes makes the development of new synthetic methods toward these compounds particularly attractive. In the past, photochemical and thermal [2+2] cycloadditions have been

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[**] EPFL, F. Hoffmann-La Roche Ltd and SNF (grant number 200021_129874) are acknowledged for financial support.
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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201303803.

most often applied to the synthesis of cyclobutanes.^[6-8] However, the scope of these transformations was limited, and harsh conditions or specialized equipment was often required. An alternative strategy based on organocatalysis was recently reported, but it remains limited to nitrocyclobutanes.^[9] Methods involving Lewis acid catalysts were successful for diverse donor–acceptor-substituted cyclobutanes.^[10,11] In the specific case of aminocyclobutanes however, there is only a single report by Avenoza and co-workers, who made use of a superstoichiometric amount of an aluminum-based Lewis acid for the synthesis of α -amino acid derivatives (Scheme 1 a).^[12] There is consequently a great need for milder catalytic methods to access differently substituted aminocyclobutanes.

a) Avenoza (Ref. [12]): α-amino esters, excess Lewis acid



b) This work: β -amino esters, catalytic Lewis acid



Scheme 1. Lewis acid catalyzed [2+2] cycloaddition for the synthesis of aminocyclobutanes. MAO = methylaluminoxane, MABR = methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide).

Herein, we report the first Lewis acid catalyzed [2+2] cycloaddition between enimides and alkylidene malonates to access β -amino acid cyclobutane derivatives (Scheme 1b). The reaction involves the use of cheap and non-toxic iron trichloride as catalyst and tolerates a wide range of substituents. The method can be used to prepare the aminocyclobutanes in gram quantities. The synthetic potential of the obtained products was demonstrated by the transformation of one of them into a β -peptide derivative, and by the first catalytic [4+2] cycloaddition of aminocyclobutane proceeding without loss of the precious nitrogen atom.

We recently reported that di(alkoxycarbonyl)-substituted cyclopropanes were stable, yet still reactive as formal dipoles when substituted by a phthalimide.^[13] We wondered if similarly substituted aminocyclobutanes would display the same reactivity. Consequently, commercially available *N*-

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Table 1: Optimization of the [2+2] cycloaddition.

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Entry	Catalyst (mol%)	<i>t</i> [h]	Malonate	т [°С]	Ratio of 6/4 ^[a]
1	ZnBr ₂ (100) ^[b]	1	5 a	-78	0:1
2	Yb(OTf) ₃ (10) ^[b]	0.75	5 a	-78	0:1
3	Sc(OTf) ₃ (10) ^[b]	0.75	5 a	-78	tr. of 6
4	Sc(OTf)₃ (10) ^[b]	0.75	5 a	-30	1:2
5	Sc(OTf) ₃ (10) ^[b]	0.5	5 a	0	1:0
6	Sc(OTf) ₃ (20) ^[c]	12	5 b	RT	0:1
7	In(OTf) ₃ (20) ^[c]	12	5 b	RT	1.5:1
8	$FeCl_3 \cdot Al_2O_3 (20)^{[c]}$	12	5 b	RT	1:0

[a] Monitored by ¹H NMR spectroscopy. [b] Known procedures were followed.^[5] [c] Lewis acid (0.2 equiv), dimethyl 2-ethylidenemalonate (**5 b**, 1 equiv) and 2-vinylisoindoline-1,3-dione (**4 a**, 1.2 equiv) added dropwise, CH_2Cl_2 , 0.1 mM. Phth = phthaloyl, tr. = traces

vinyl phthalimide (4a) and methylidene malonate 5a were chosen as reaction partners to attempt the synthesis of aminocyclobutane 6aa (Table 1). The use of the conditions reported for the synthesis of carbo- or alkoxy-substituted cyclobutanes^[5] did not give the desired product (entries 1–3). Nevertheless, when scandium triflate was used as catalyst, traces of the product could be detected by ¹H NMR spectroscopic analysis of the crude product (entry 3) and by increasing the reaction temperature, a complete conversion could be observed (entries 4 and 5). In this case, the major product was the desired cyclobutane 6aa. At a higher temperature than 0°C, degradation of starting material 4a as well as product 6aa was observed. In order to test this system with less reactive substrates, commercially available ethylidene malonate **5b** was reacted with **4a** in the presence of scandium triflate at room temperature (entry 6). As no conversion was achieved in this case, other Lewis acids were examined for the [2+2] cycloaddition. Indium triflate and iron trichloride supported on alumina^[14] were able to catalyze the reaction, even if full conversion was not achieved with the former Lewis acid (entries 7 and 8).^[15] Based on these preliminary results, the iron catalyst was selected to study the scope of the reaction.

On preparative scale, iron trichloride on alumina was also a good catalyst (10 mol%) for the reaction between **4a** and unsubstituted methylidene malonate **5a** (Scheme 2). Variation of the nitrogen substituent was first examined.^[16] Succinimide as well as maleimide were tolerated, giving the cyclobutanes **6ba** and **6ca** in 91% and 48% yield, respectively. The reaction also allowed the formation of Bocprotected thymine cyclobutane **6da** in 76% yield. The use of an N-vinyl oxazolidinone failed to deliver product **6ea** as a result of decomposition of the starting material. Cycloaddition of keto ester substrates was possible, affording cyclobutane **6ac** in 62% yield.

At this point, we turned to the synthesis of aminocyclobutanes with multiple substituents. The use of (E)-substituted



Scheme 2. Scope of the [2+2] cycloaddition with methylidene dicarbonyl compounds. Reaction conditions: enimide (0.20 mmol, 1 equiv), alkylidene malonate (0.40 mmol, 2 equiv), Fe catalyst (1 mmol g^{-1} , 20 mg, 0.020 mmol, 0.1 equiv) in CH₂Cl₂ (1 mL) for 0.2–5 h. [a] 4 equiv of methylidene malonate were used. [b] b.r.s.m., 50% yield of isolated product. [c] b.r.s.m., 38% yield of isolated product. b.r.s.m.=based on recovered starting material, Boc=*tert*-butoxycarbonyl, E=CO₂Me, Succ=succinyl.

enimides^[17] was examined first. Enimides substituted with a methyl, hexyl, or cyclopropyl group afforded the corresponding cyclobutanes 6 fa, 6 ga, and 6 ha in 74-85 % yield. An aliphatic chloro substituent was also compatible with the reaction conditions (product 6ia). Succinimide-substituted cyclobutanes 6ja and 6ka could also be obtained in 81 and 83% yield, respectively. Importantly, in all the experiments that involve the use of (E)-substituted enimides (except for the formation of cyclobutane 6ka), only one cyclobutane diastereoisomer could be detected in the crude mixture of the reaction. Aromatic substitution of the enimide was next investigated. The reaction delivered a single diastereoisomer of cyclobutane 6la bearing a phenyl substituent in 90% yield. A para-bromo substituent on the benzene ring slowed down the reaction and full conversion to cyclobutane 6ma was not observed. However, decreasing the conjugation of the benzene ring with the enimide by moving the bromine atom to the *ortho* position^[18] restored the reactivity, and product **6na**



could be obtained in 93% yield. Finally, the reaction was slower in the presence of a trifluoromethyl group, but cyclobutane 60a could still be obtained in 38% yield (45% based on recovered starting material).

When we switched to electron-rich aromatic rings as substituents, we observed a different regioselectivity (Scheme 3). When tolyl-substituted enimide **4p** was used, a 2.5:1 mixture of "normal" and "inverted" products **6pa** and **6pa**' was obtained (Scheme 3a). *p*-Methoxybenzene-substi-



Scheme 3. [2+2] Cycloaddition with enamides substituted with electron-rich benzene rings. Tol = tolyl.

tuted substrate **4q** gave only the "inverted" product **6qa**' (Scheme 3b). This switch in regioselectivity is interesting as it gives access to equally important γ -amino acid cyclobutane derivatives.^[19] Additionally, it allowed the assignment of the relative donating ability of the phthaloyl group compared to electron-rich aromatic groups in the [2+2] cycloaddition, which may also be useful in future for the design of other transformations.

Less reactive substituted alkylidene malonates^[20] also afforded cyclobutanes **6ab**, **6ad**, and **6ae** in 59–71 % yields, but usually without diastereoselectivity (Scheme 4).^[21] The use of benzyl-substituted alkylidene malonates **5 f** allowed the formation of product **6af** in a better diastereomeric ratio of 3:1 and 62 % yield. In the case of trifluoromethyl-substituted aminocyclobutane **6ag**, only the *trans* diastereoisomer was obtained in 76 % yield. This is an important result, as methods for the synthesis of trifluoromethyl-substituted aminocyclobutanes are rare, require numerous steps, and usually lack diastereoselectivity.^[6b,22]

Methylidene malonates such as **5a** are very reactive compounds and start to decompose after a few days, even when stored under argon at -20 °C. The access to these building blocks involves a complex Knoevenagel/Diels– Alder/recrystallization/cracking sequence followed by a base-sensitive distillation in paraffin.^[23] This difficult access to methylidene malonates was a serious limitation for the preparative use of our [2+2] cycloaddition methodology. We found that the method developed by Connell and coworkers for the methenylation of dicarbonyl compounds^[20b] could be adapted to the synthesis of the sensitive methylidene malonates (Scheme 5). When the reaction was completed, the crude mixture could be used directly in the cycloaddition reaction. The efficacy of this method was demonstrated by



Scheme 4. Scope of the [2+2] cycloaddition with alkylidene malonates. Reaction conditions: Enimide (0.20 mmol, 1 equiv), alkylidene malonate (0.40 mmol, 2 equiv), Fe catalyst (1 mmol g^{-1} , 20 mg, 0.020 mmol, 0.1 equiv) in CH₂Cl₂ (1 mL). Cy=cyclohexyl.



Scheme 5. Gram-scale synthesis of aminocyclobutanes.

accessing cyclobutanes **6aa**, **6ah**, **6ai**, and **6fa** within a few hours from commercially available starting materials on a gram scale using a catalyst loading of 5 mol%.

In order to better understand the reaction mechanism, it would be important to know whether the reaction is stereospecific in relation to the geometry of the enamide, or whether the observed high *trans* diastereoselectivity is due only to thermodynamic control. When (Z)-substituted enimides were used, no conversion was detected, even after prolonged reaction times. The lack of reactivity in the case of the (Z)-substituted isomer could be tentatively attributed to the loss of conjugation between the p orbital of the nitrogen atom and the π system of the olefin as a result of steric interactions, thus leading to lower nucleophilicity. To answer the question of stereospecificity, deuterated enimide 4r was synthesized^[24] and submitted to the reaction conditions (Scheme 6). Only a slight loss of stereoinformation was observed during the reaction. This result supported a stepwise mechanism via a zwitterionic intermediate A, but also indicated a fast ring closure, which could compete with single-bond rotation.

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Scheme 6. Reaction with deuterated enamide **4r** and speculative zwitterionic intermediate **A**.

Finally, we selected two key transformations to highlight the potential of aminocyclobutanes both as synthetic precursors and as structural units (Scheme 7). The reaction of aminocyclobutane **6aa** with enol silane **9** catalyzed by tin tetrachloride afforded one diastereoisomer of aminocyclohexane **10** in 95% yield (Scheme 7a). To the best of our knowledge, this is the first report of such a formal [4+2] cycloaddition^[25] between an aminocyclobutane and an olefin.



Scheme 7. Formal [4+2] cycloaddition and synthesis of dipeptide 11.

The conversion of cyclobutane **6ai** to glycine–dipeptide **11** was achieved in three steps with an overall yield of 78% (Scheme 7b).^[26]

In conclusion, we have developed the first Lewis acid catalyzed [2+2] cycloaddition for the synthesis of β -amino acid cyclobutane derivatives. The reaction gave access to cyclobutanes with multiple substituents, including important derivatives for medicinal chemistry, such as nucleoside analogues or trifluoromethylated compounds. A simplified access to highly sensitive methylidene malonates was also developed, allowing the gram-scale synthesis of aminocyclobutanes. The synthetic potential of the obtained aminocyclobutanes was demonstrated by the transformation of one of them to a β -peptide derivative and by a catalytic [4+2] annulation reaction for the synthesis of cyclohexylamines.

Received: May 3, 2013 Published online:

Keywords: aminocyclobutanes \cdot cycloaddition \cdot cyclobutanes \cdot iron

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malonate, a new one-step synthesis was developed instead of the known tedious three-step method.^[20e] See the Supporting Information for more details.

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- [24] 4r was synthesized by reduction of the deuterated ynimide with Lindlar catalyst. See the Supporting Information for further details.
- [25] As the reaction between cyclobutane 6aa and silyl enol ether 9 involves a C–C bond cleavage, the reaction is best described as a "formal cycloaddition", in contrast to the [2+2] cycloaddition. See also the discussion in reference [13c].
- [26] Cleavage of the phthaloyl group from product 10 occurred smoothly in 87% yield using diaminoethane as reagent. In contrast, cleavage of the phthaloyl group from cyclobutane 11 was not possible in a good yield. Alternative synthetic routes to generate the free cyclobutylamines are currently under investigation.

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