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[8+2] Formal Cycloaddition Reactions of Tropones with Azlactones under Brønsted Acid Catalysis and Synthesis of α-(2-Tropyl), α-Alkyl α-Amino Acids

Francisco Esteban,[a] Ricardo Alfaro,[a] Francisco Yuste,[a] Alejandro Parra,[a] José Luis García Ruano,*[a] and José Alemán*[a]

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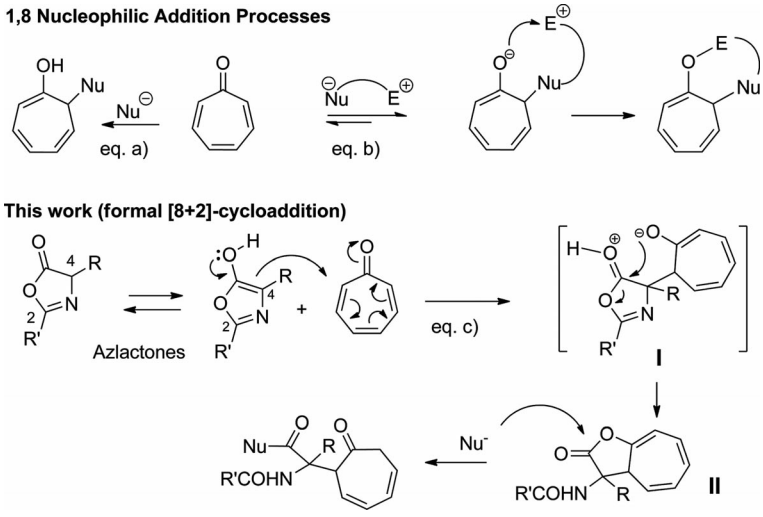
The reaction of tropones with azlactones catalyzed by Brønsted acids affords a variety of dihydro-2*H*-cyclohepta-[*b*]furan derivatives, corresponding to a formal [8+2] cycloaddition process. They can easily be opened by nucleophiles to afford a new type of α,α-disubstituted α-amino acid (or peptide) containing seven-membered rings at the quaternary position.

Introduction

The nonbenzenoid aromatic structure of tropones and troponoids has attracted the attention of chemists in the last decades from a theoretical and synthetic point of view.[1] These structures have been found and used in the total synthesis of natural products,[2] and their behavior in cycloaddition reactions has been widely studied as an idoneous π system for the investigation of the competition between different types of reactions.[3] Other aspects concerning their reactivity, such as nucleophilic additions, have also been studied,[4] and most of them have involved 1,8-addition processes (Scheme 1, equation a). One of the most interesting reactions of the tropones occurs with reagents that simultaneously contain nucleophilic and electrophilic centers. They are tandem processes involving an initial nucleophilic attack at C-2 of the tropone ring (1,8-addition) followed by an intramolecular reaction of the resulting enolate with the electrophilic center of the reagent (Scheme 1, equation b). Precursors of different 1,3-dipoles have been used in these reactions to afford bicyclic structures that formally correspond to [8+2][5] and [6+3][6] cyclo-



Scheme 1. Different reactivities of tropone derivatives.

additions processes,[7] but the use of azlactones in this type of reaction has never been explored.

At this point, we hypothesized about the reactions of tropones with azlactones because they are stable compounds that exhibit dual electrophilic (carbonylic carbon atom) and nucleophilic (C-2 or C-4) behavior. The C-4

[a] Departmento de Química Orgánica (módulo 1), Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain
E-mail: jose.aleman@uam.es
www.uam.es/JLGR

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nucleophilic attack of the azlactone at the electrophilic C-2 of the tropone ring (1,8-nucleophilic addition) would generate the enolate **I**, which facilitates the intramolecular opening of the oxazolone ring by the enolate oxygen atom to afford lactones **II** (a formal [8+2] cycloaddition reaction). These lactones would be interesting precursors of N-protected quaternary amino acid derivatives, which could eventually be incorporated into peptide chains.[8] Moreover, the peptide would contain an unusual seven-membered ring located at C-α, easily obtained in reactions with oxygenated or nitrogenated nucleophiles, that could be used to introduce other functionalities into the peptides. The importance of quaternary amino acids and the peptides containing them[9] justifies the search for new synthetic methods, a field in which azlactones have played a relevant role.[10] In this work, we report the results obtained in the reaction of tropones with azlactones catalyzed by Brønsted acids and the use of the resulting lactones in the synthesis of new α,α-disubstituted α-amino acids bearing seven-membered rings at the quaternary center.

Results and Discussion

We first studied the reaction of tropone (**1A**) with the azlactone **2a** in CH_2Cl_2. After several hours at room temperature, no reaction occurred (Scheme 2), but in the presence of catalytic amounts of acids or bases (which presumably activate the tropone or the azlactone, respectively), mixtures of the bicyclic lactones **3Aa** and **3′Aa** are found. Thus, under diphenylphosphoric acid catalysis (dpp, 10 mol-%), the reaction gave full conversion to a 75:25 mixture of **3Aa**/**3′Aa** after 1 h at room temp. (Scheme 2). However, in the presence of Et_3N (10 mol-%), the reaction required longer reaction times (5 h at room temp.) for completion and afforded a 36:64 mixture of the same lactones with **3′Aa** as the major diastereoisomer (Scheme 2). Crystallization of **3Aa** allowed its unequivocal assignment as the *S**,*S** isomer by X-ray analysis (see Figure 1).[11]

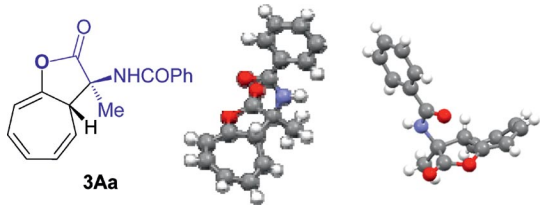
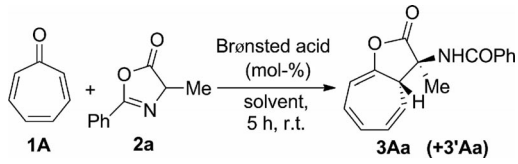


Figure 1. Two different views of **3Aa** obtained by X-ray analysis.

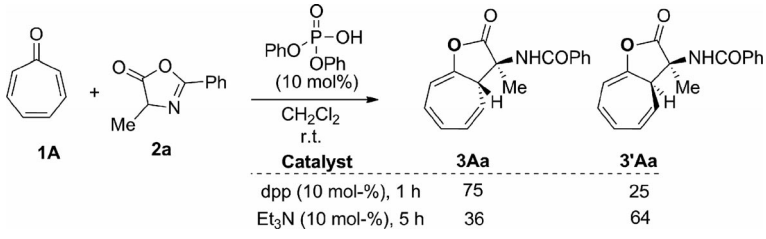
Results of Scheme 2 indicate that the acidic catalysis is more efficient (better reactivity and stereoselectivity control), which prompted us to optimize these reactions (Table 1). We first found that the reaction of **1A** with **2a** occurred in 5 h in the presence of 5 mol-% of dpp without a significant effect on the diastereomeric ratio of **3Aa** and **3′Aa** (70:30; Table 1, Entry 1). Then, we studied the influence of other Brønsted acids (5 mol-%) on the reaction course. Complete conversion was also observed after 5 h by using (+)-camphorsulfonic acid and trifluoroacetic acid (TFA; Table 1, Entries 4 and 5), whereas lower conversions were obtained in the presence of BzOH and *p*-toluenesulfonic acid (TsOH; Table 1, Entries 2 and 3). As the best diastereomeric ratio (*dr*) was obtained with TFA (77:23; Table 1, Entry 5), this acid was used for further optimization. Diastereoselectivity and reactivity were influenced by the solvent. Thus, the conversions were not complete after 5 h in tetrahydrofuran (THF) and $CHCl_3$, and lower diastereoselectivities than those in CH_2Cl_2 were obtained (Table 1, Entries 6 and 7). In toluene and *p*-xylene, complete conversion and a better *dr* were obtained (Table 1, Entries 8 and 9). The use of a lower amount of catalyst (1 mol-

Table 1. Screening results for the addition of **2a** to tropone **1A**.[a]



Entry	Catalyst (mol-%)	Solvent	*dr*[b]	Conversion [%]
1	dpp (5)	CH_2Cl_2	70:30	100
2	BzOH (5)	CH_2Cl_2	70:30	83
3	TsOH (5)	CH_2Cl_2	76:24	65
4	CSA[c] (5)	CH_2Cl_2	73:27[d]	98
5	TFA (5)	CH_2Cl_2	77:23	100
6	TFA (5)	THF	65:35	86
7	TFA (5)	$HCCl_3$	71:29	90
8	TFA (5)	toluene	85:15	100
9	TFA (5)	*p*-xylene	93:7	100 (95)[e]
10	TFA (1)	*p*-xylene	90:10	85[f]
11	TFA (5)	CH_2Cl_2	81:19	25[g, h]

[a] All reactions were performed with **1A** (0.1 mmol), **2a** (0.12 mmol), and solvent (0.3 mL). [b] Diastereomeric ratio determined by ^1H NMR spectroscopy. [c] Camphorsulfonic acid. [d] Compound **3Aa** was nearly racemic. [e] Combined isolated yield. [f] Conversion after 24 h. [g] Reaction was performed at 0 °C. [h] Conversion after 48 h.

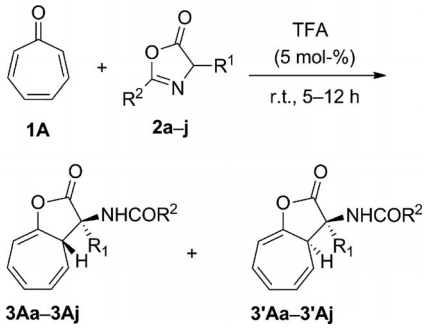


Scheme 2. Reaction of the tropone **1A** with the azlactone **2a** under different conditions.

%) substantially decreased the reactivity (85% conversion was observed after 24 h; Table 1, Entry 10), and a decrease in the reaction temperature (0 °C) slightly improved the *dr*, but there was only moderate conversion after 48 h (Table 1, compare Entries 5 and 11).[12]

Under the best conditions (Table 1, Entry 9), we studied the scope of the reaction of **1A** with azlactones derived from different amino acids (**2a**–**2j**; Table 2). The reactions with azlactone derivatives with linear alkyl chains, such as those from alanine (R^1 = Me, **2a**), norvaline (R^1 = *n*Pr, **2b**), and homophenylalanine (R^1 = CH_2CH_2Ph, **2c**), led to lactones **3Aa**–**3Ac** in excellent yields (>95%) and good diastereoselectivities (Table 2, Entries 1–3). Similar results were obtained for the reaction of **1A** with the methionine derivatives **2d** (R^1 = CH_2SCH_3, Table 2, Entry 4), **2e** (R^1 = $PhCH_2$, Table 2, Entry 5), **2f** (R^1 = $CyCH_2$, Table 2, Entry 6), and **2g** (R^1 = *i*$PrCH_2$, Table 2, Entry 7). The reaction of **1A** with **2h**, which bears a bulkier *i*Pr group at the α position, also afforded **3Ah** (*dr* up to 94:6) in slightly lower yield (70%, Table 2, Entry 8). The negative influences of the aryl groups at C-4 on the stereoselectivity (**2i**, R^1 = Ph, Table 2, Entry 9) and the alkyl groups at C-2 on the reactivity (**2j**, R^2 = Me, Table 2, Entry 10) are notable.

Table 2. Scope of the 1,8-nucleophilic addition of different azlactones **2a**–**2j** to the tropone **1A**.[a]

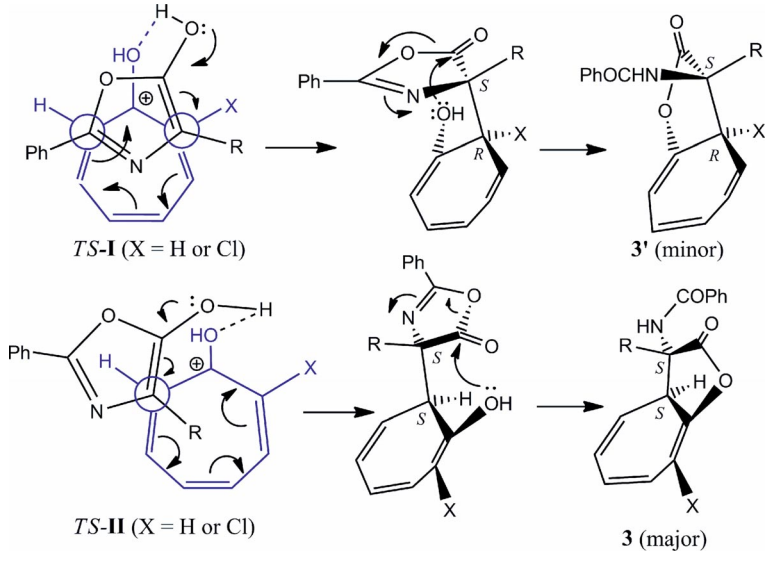


Entry	Azlactone (R^1, R^2)	*dr*[b] (**3**/**3′**)	Compound[c] (yield [%])
1	**2a** (Me, Ph)	93:7	**3Aa** (95)
2	**2b** (*n*Pr, Ph)	93:7	**3Ab** (95)
3	**2c** ($PhCH_2CH_2$, Ph)	88:12	**3Ac** (95)
4	**2d** (CH_3SCH_2, Ph)	87:13	**3Ad** (98)
5	**2e** ($PhCH_2$, Ph)	88:12	**3Ae** (89)
6	**2f** ($CyCH_2$, Ph)	81:19	**3Af** (76)
7	**2g** (*i*$PrCH_2$, Ph)	86:14	**3Ag** (91)
8	**2h** (*i*Pr, Ph)	94:6	**3Ah** (70)
9	**2i** (Ph, Ph)	62:38	**3Ai** (92)
10	**2j** (Me, Me)	85:15	**3Aj** (32)

[a] All reactions were performed with **1A** (0.1 mmol) and **2** (0.12 mmol) in xylene (0.3 mL). [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Combined isolated yield.

The stereoselectivity can be explained by assuming that a hydrogen bond is initially formed between the OH group of the enol (which acts as a nucleophile in acidic medium) and the oxygen atom of the protonated tropone (activated electrophile).[13] Now, two possible transition states (TS-**I** and TS-**II**, Scheme 3), which differ in the diastereotopic carbon atom (C-α in TS-**I** or C-α′ in TS-**II**) that is attacked by the enol nucleophile, can be postulated. TS-**I** must be destabilized with respect to TS-**II** because of the steric interactions, and this determine the predominance of the *S**,*S** isomer in the reaction mixture. The evolution of the resulting intermediates by intramolecular opening of the azlactone rings affords the lactones **3** (major) and **3′**.

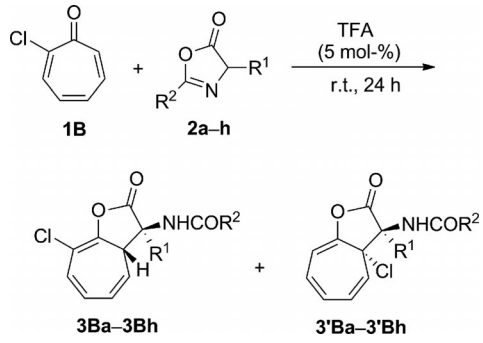
We hypothesized that the incorporation of a substituent at the α-position (e.g., Cl) should have a significant influence on the chemoselectivity because it would produce an additional destabilization of **I** (with the Cl/R interaction instead of H/R) without affecting **II**, which would favor even more the prevalence of **3** with respect to **3′**. In addition, the incorporation of a chlorine atom at the α-position of the tropone ring would be interesting because its elimination could generate quaternary amino acids with tropone rings at C-α. The results obtained in the reactions of the α-



Scheme 3. Possible transition states in the reaction of protonated tropones with azlactones.

chlorotropone (**1B**) with the azlactones **2a**, **2b**, and **2f**–**2h** are indicated in Table 3. The reactivity of **1B** was lower than that of **1A**, and 24 h was required for full conversion.[14] The chemoselectivity was completely controlled, and only the diastereomerically pure products **3Ba**–**3Bj** were formed as a result of the attack at the unsubstituted α′-position. Both facts were expected owing to the previously mentioned steric repulsion produced by the chlorine atom. Additionally, the *S**,*S** configuration of **3Ba** was unequivocally assigned by X-ray analysis (Figure 2),[15] which supports the mechanism suggested in Scheme 3.

Table 3. Scope for the 1,8-Michael addition of different azlactones **2a**–**2h** to the tropone **1B**.[a]



Entry	Azlactone (R^1, R^2)	**3/3′**[b]	Compound (isolated yield [%])
1	**2a** (Me, Ph)	>98:<2	**3Ba** (97)
2	**2a** (Me, Ph)	>98:<2	**3Ba** (98)[c]
3	**2b** (*n*Pr, Me)	>98:<2	**3Bb** (97)
4	**2f** ($CyCH_2$, Ph)	>98:<2	**3Bf** (87)
5	**2g** (*i*$PrCH_2$, Ph)	>98:<2	**3Bg** (93)
6	**2h** (*i*Pr, Ph)	>98:<2	**3Bh** (72)

[a] All reactions were performed with **1B** (0.1 mmol) and **2** (0.12 mmol) in *p*-xylene (0.3 mL). [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction performed on 1.0 mmol scale.

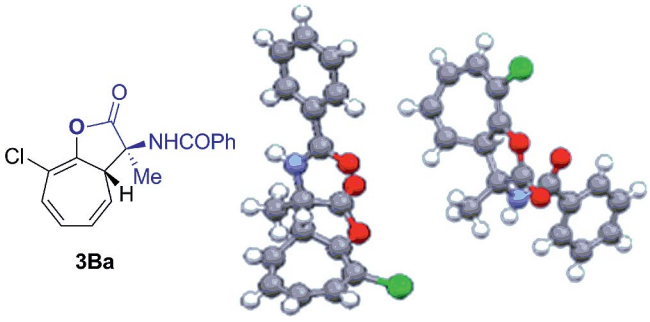
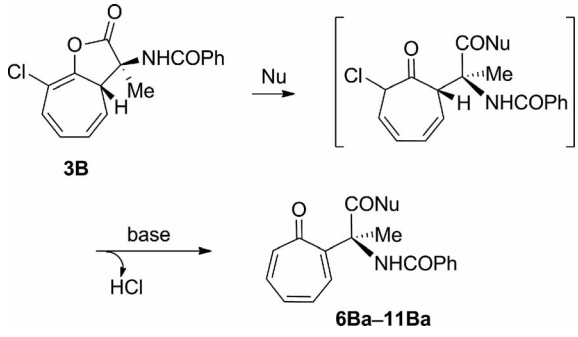


Figure 2. Two different views of compound **3Ba** obtained by X-ray analysis.

Once we had obtained these dihydro-2*H*-cyclohepta[*b*]-furan derivatives **3**, we studied their behavior with different nucleophiles. The reaction of **3Aa** with MeOH/K_2CO_3 afforded the α,α-dimethyl cycloheptadienone α-aminomethyl ester **4Aa** in only 20 min at –20 °C (88% yield), presumably owing to the protonation of the enolate **III** formed in the ring-opening reaction (Scheme 4). Similar behavior was observed for the reaction of **3Aa** with glycine methyl ester, which afforded **5Aa** in good yield (60%).[16]

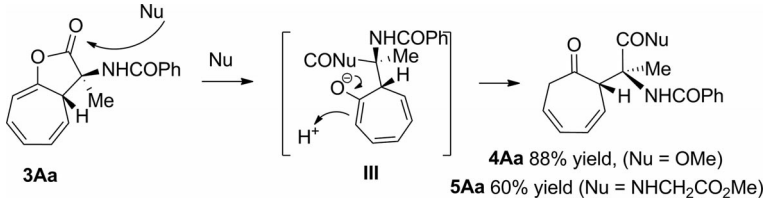
The results obtained in the reaction of the chloro derivative **3B** with different nucleophiles were more interesting (Table 4). In this case, the product of the nucleophilic opening of the lactone ring is subsequently dehydrohalogenated with another molecule of the nucleophile acting as a base or with an external base (K_2CO_3). The reactions with MeOH, *i*$PrNH_2$, and glycine afforded only one α-(2-tropyl), α-alkyl amino acid derivative (Table 4, Entries 1–3). Homochiral amino acids gave separable diastereoisomeric mixtures of enantiomerically pure dipeptides that differed in the configuration at the quaternary carbon atom (Table 4, Entries 3–8).[17] Owing to the lower reactivity of α-substituted amino acids, we studied different reaction conditions with 1.0 and 4.0 equiv. of the Ala-OBn amino acid and also with an external base (1.0 equiv. of K_2CO_3). We found higher yields with 4 equiv. (Table 4, Entries 4 and 6)[18] than with 1 equiv.

Table 4. Synthesis of esters and amides from lactones **3B**.[a]



Entry	Nucleophilic reagent (equiv.)	Products (isolated yield [%])
1	MeOH (1)[b]	**6Ba** (95)
2	*i*$PrNH_2$ (1)[b]	**7Ba** (70)
3	Gly-OMe (4.5)	**8Ba** (100)
4	Ala-OBn (4)	**9Ba**(43)/**9′Ba**(35), (90)[a]
5	Ala-OBn (1)	**9Ba**/**9′Ba**(60)[a]
6	Ala-OBn (4)[b]	**9Ba**/**9′Ba**(98)[a]
7	PhAla-OBn (4)[b]	**10Ba**/**10′Ba**(81)[a]
8	Val-OBn (4)	**11Ba**/**11′Ba**(47)[a]

[a] Combined yield. [b] 1.0 equiv. of K_2CO_3 was used.



Scheme 4. Synthesis of esters and amides from lactone **3Aa**.

(Table 4, Entry 5) and a higher reaction rate when a cobase (K_2CO_3) was added. In the case of alanine, we were able to separate the diastereomeric mixture; therefore, this methodology allows the isolation of optically pure dipeptides (**9Ba** and **9′Ba**; Table 4, Entry 4). Other amino acids such as phenylalanine or valine provided similar results although with a slightly lower yield for the bulkier valine derivative (Table 4, Entries 7 and 8).

Conclusions

We have found a new approach for the synthesis of a variety of dihydro-2*H*-cyclohepta[*b*]furan derivatives by reaction of tropones and azlactones under Brønsted acid catalysis. They can easily be opened with nucleophiles to form α,α-disubstituted amino acids (or dipeptides) bearing seven-membered rings at the quaternary carbon atoms. The use of homochiral amino acids as nucleophiles provides separable mixtures of enantiomerically pure α-(2-tropyl), α-alkyl α-amino acid dipeptides.

Experimental Section

General Methods: NMR spectra were acquired with a Bruker 300 spectrometer at 300 and 75 MHz for ^1H and ^{13}C, respectively. Chemical shifts are reported in ppm relative to residual solvent signals ($CHCl_3$, δ = 7.26 ppm for ^1H NMR, $CDCl_3$, δ = 77.0 ppm). ^{13}C NMR spectra were acquired in broadband-decoupled mode. Analytical thin layer chromatography (TLC) was performed by using precoated aluminium-backed plates (Merck Kieselgel 60 F254), and the plates were visualized by ultraviolet irradiation or $KMnO_4$ dip. Purification of reaction products was performed by flash chromatography (FC) with silica gel Merck-60 or Fluorisil® 100–200 mesh. Materials: Commercially available tropones **1A** and **1B** and chiral phosphoric acids were used without further purification. Azlactones **2a**, **2c**–**2f**, and **2h**–**2j** were synthesized according to literature procedures.[19]

General Procedure for the Synthesis of 3Aa–3Aj and 3Ba–3Bh: To an ordinary vial charged with azlactone **2** (012 mmol) was added the corresponding tropone **1A** or **1B** (0.1 mmol) and TFA (5 mol-%) in *p*-xylene (0.3 mL) at room temp. Once the reaction was finished (as monitored by ^1H NMR spectroscopy, usually 5–12 h), the solvent was eliminated under reduced pressure, and the residue was directly collected by filtration to afford the pure products.

***rac*-*N*-[(3*S*,3a*S*)-8-Chloro-3-methyl-2-oxo-3,3a-dihydro-2*H*-cyclohepta[*b*]furan-3-yl]benzamide (3Ba):** The product was obtained as a unique diastereoisomer by following the standard procedure with tropone **1B** and azlactone **2a** to afford a white solid (97% yield), m.p. 217–219 °C. ^1H NMR (300 MHz, [D$_6$]acetone): δ = 8.52 (br s, 1 H), 7.92 (dd, J = 3.1, 1.1 Hz, 2 H), 7.59–7.55 (m, 1 H), 7.49–7.46 (m, 2 H), 6.36 (d, J = 1.8 Hz, 2 H), 6.26–6.22 (m, 1 H), 5.64 (dd, J = 3.9, 2.2 Hz, 1 H), 3.64–3.63 (m. 1 H), 1.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 174.4, 167.8, 142.7, 133.5, 132.9, 129.5, 129.2, 128.4, 128.1, 128.0, 121.7, 106.4, 59.7, 46.2, 20.3 ppm. HRMS (ESI+): calcd. for $C_{17}H_{14}ClNO_3$ $[M + H]^+$ 315.0713; found 315.0721.

Supporting Information (see footnote on the first page of this article): Characterization data for all compounds. Copies of the ^1H and ^{13}C NMR spectra for the final products.

Acknowledgments

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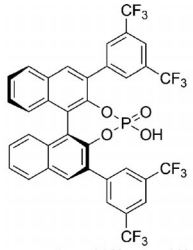
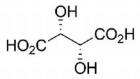
[11] CCDC-913779 (for **3Aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] Initial trials with different enantiomerically pure acids were unsuccessful in transferring chirality, and only moderate enantiomeric excesses (up to 15%*ee*) were found.



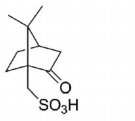
conversion >99%, *ee* = 0%

conversion >99%, *ee* = 9%



conversion >99%, *ee* = 8%

conversion >99%, *ee* = 15%



conversion 98%, *ee* = 4%

[13] Alternatively, the mechanism might involve *N*-protonation of the azlactone, which makes enolization and ionization to a neutral (mesoionic) azomethine ylide easier.

[14] This lower reactivity can be improved by increasing the amount of the catalyst to 20 mol-%, but a decrease in the stereoselectivity was also observed.

[15] CCDC-947015 (for **3Ba**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] The reaction of the alanine methyl ester with **3Aa** resulted only in decomposition of the tropone after several days of reaction.

[17] Under kinetic resolution conditions (0.6 equiv. Ala-OBn), a mixture of isomers (ca. 2:1) was formed in reactions of **3Ba** but with lower yield.

[18] The excess amino acid can be quantitatively recovered by using a SCX column.

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