[6] $C_{10}H_{24}N_4O_6Pd_2 \cdot 7H_2O$, $M_r = 635.27$, yellow rod, $0.09 \times 0.05 \times 0.02$ mm, monoclinic, space group $P2_1$, $a = 8.3451(4)$, $b = 8.8020(5)$, $c = 15.2168(9)$ Å, $b = 93.937(3)^\circ$, $V = 1115.09(11)$ Å^3, $Z = 2$, $\rho = 1.8920(2)$ g cm^{-3}, $2\theta_{max} = 55^\circ$, $Mo_{K\alpha}$, $\lambda = 0.71073$ Å, Stoe IPDS, $T = 200$ K, 8220 reflections, 4283 independent and used in refinement, direct methods (SHELXS), full-matrix least squares against F^2 (SHELXL), 256 parameters, H in calculated positions, $R(F) = 0.180$, $R_w(F^2) = 0.200$, max. difference electron density 1.6 e Å^{-3}, Flack parameter $-0.01(11)$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-159804. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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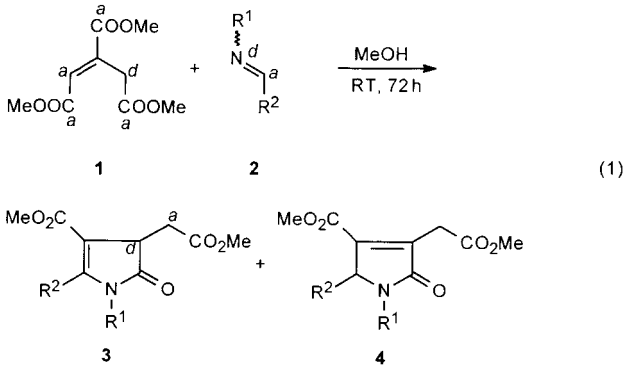


	R^1	R^2	Yield [%]	**3:4**
a	Benzyl	Phenyl	57	100:0
b	Benzyl	Naphthyl	55	0:100
c	Benzyl	*o*-Hydroxyphenyl	28	38:62
d	2-Furylmethyl	Phenyl	52	100:0
e	Methyl	Phenyl	46	41:59

Heterocycles through Domino Reactions with Trimethyl Aconitate, a Versatile Synthetic Building Block**

Daniel Witthaut, Roland Fröhlich,[+] and Hans J. Schäfer*

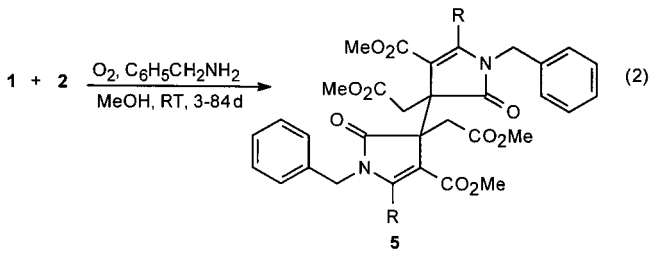
Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

Selective C–C bond formations require building blocks of opposite reactivity, that is donors and acceptors. Anionic donors, which are soluble in methanol, simplify thereby the performance of the reaction. Trimethyl aconitate (**1**), a C_6 building block, is of interest in this regard. It possesses five functional groups: one donor, namely the acidic methylene group of a vinylogous malonate and four acceptors, namely the electrophilic double bond and three ester groups. Furthermore aconitic acid is a renewable raw material, which can be extracted from sugar molasses or be obtained by dehydration of citric acid. In spite of these favorable presuppositions **1** has up to now been rarely used in synthesis.[1] First systematic investigations demonstrate that the functional groups in **1** can be used for Michael additions,[2] Diels – Alder cycloadditions,[3] Knoevenagel condensations,[4] and cyclodimerizations.[5] Here we report on domino reactions[6] of the donor(*d*) and acceptor(*a*) groups of **1** with imines.

Stirring equimolar amounts of **1** with the imine **2** in methanol leads to the dihydropyrrolones **3** and **4** [Eq. (1)]. The isomer **4** was shown by AM1 and PM3 calculations to be thermodynamically more stable than **3**. For the product formation the following reaction path appears plausible: **1** reacts with one equivalent of imine in a domino reaction, which consists of a nucleophilic addition, an intramolecular acylation, and a shift of the exocyclic double bond, to form the 2,5-dihydropyrrolone **3**. The subsequent base-catalyzed double bond shift leading to **4** is evidently kinetically controlled by the substituents R^1 and R^2.

2,5-Dihydropyrrolones **3** are components of herbicides[7] and structural motifs of natural products.[8] They are usually prepared by reaction of enaminoesters or imines, respectively, with dialkyl maleates or maleic anhydride leading to N1 – C2 and C4 – C5 connections.[9] The alternative N1 – C2 and C4 – C5 connection established here using **1** and imines allows a simpler variation of the C5 substituent in the dihydropyrrolone.

The reaction of **1** with the imine **2a** in the presence of benzylamine leads to the bisdihydropyrrolone **5a** [Eq. (2)], which is obtained nearly exclusively as the racemate as shown by the crystal structure analysis.



	R	Yield [%]
a	Phenyl	43
b	Naphthyl	35
c	*o*-Hydroxyphenyl	39

As the reaction does not occur when using triethylamine, benzylamine evidently acts as redox-mediator and not as base. Benzylamine is possibly oxidized by air to the cation radical, which is deprotonated to the benzylamino radical. This radical could abstract a hydrogen atom from the simultaneously

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[+] Crystal structure analysis

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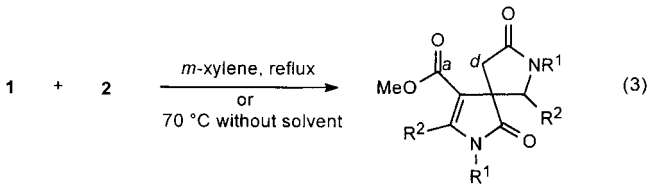
formed 2,5-dihydropyrolone **3** to form a hydropyrrolone radical which then dimerizes to give product **5a**. The intermediate hydropyrrolone radical is a captodative stabilized[10] allyl radical similar to the stable 4-carbomethoxypyridinyl radical.[11] This domino reaction consisting of an imine addition, an intramolecular acylation, and an oxidative coupling can be transferred to the imines **2b** and **2c**. When used in excess the imines evidently act as redox-mediators themselves making the presence of benzylamine no longer necessary. The bisdihydropyrrolones **5** contain the structural motif of dimer indole alkaloids.[12] They are prepared by 3,3-coupling of appropriate precursors, and in most cases are obtained in low yields due to the steric hindrance associated with forming bonds between the quarternary C3 atoms. An exception is the dimerization of an oxindole enolate with tetraiodomethane, which presumably occurs via an anion-radical mechanism and forms the key step of a folicanthine synthesis.[13]

The spiro[pyrrolidinone-3,3′-dihydropyrrolinone] **6** is obtained in a one-pot reaction from **1** and two equivalents of **2** in refluxing xylene or at 70 °C without solvent [Eq. (3)]. The



(3)

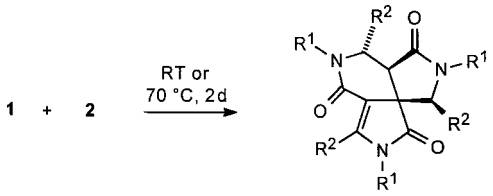
6

2	6	R^1	R^2	Yield [%]	d.r.[18]
e	**a**	Methyl	Phenyl	40	2:1
f	**b**	Methyl	*p*-Methoxyphenyl	41	5:2
g	**c**	Methyl	*p*-Chlorophenyl	44	3:1
h	**d**	Methyl	*o*-Chlorophenyl	38	5:4
i	**e**	Methyl	1*H*-Indol-3-yl	35	5:4
j	**f**	Ethyl	*o*-Chlorophenyl	36	2:1:1

formation of **6** can be explained by a base-catalyzed addition of the intermediate dihydropyrrolone **3** or **4** to the imine and a subsequent intramolecular acylation of the amino group with a second ester group in **1**.[14] Up to now there are only a few routes to the structural motif in **6**.[15] Spiro[pyrrolidine-3,3′-oxindoles] are potential cytostatica,[16a] spiro[succinimide-3,3′-isooxindole] exhibits an antidiabetic activity.[17]

The reaction of **1** with **2g** afforded **6c** in 44 % yield together with the tricyclic spiro compound **7a** in 1 % yield, showing that the remaining reactive acceptor in **6** and the donor of trimethyl aconitate can still react with the imine. When three equivalents of other imines are allowed to react with **1** two further tricyclic spiro compounds are obtained in higher yields [Eq. (4)]. Even though eight diastereomers are conceivable, the crystalline compounds **7b** and **7c** are isolated as one racemic diastereomer in each case (one enantiomer is shown). To our knowledge compounds with the structural motif of **7** have not been described before.

The formation of **7** can be interpreted by a base-catalyzed addition of the intermediate **6** to the imine and subsequent acylation of the amino group by the remaining third ester group. Thus, the C,H-acidic methylene group and the three



(4)

rac-**7**

2	7	R^1	R^2	Yield [%]
g	**a**	Methyl	*p*-Chlorophenyl	1
e	**b**	Methyl	Phenyl	7
k	**c**	Methyl	Pyridin-2-yl	17

ester groups in **1** have been used for product formation. As **7** is formed in a domino reaction that consists of three imine additions with subsequent intramolecular acylation, the yield per step leading to **7c** averages between 70 and 80 %.

Trimethyl aconitate, a cheap renewable raw material that up to now has only been scarcely used as C_6 building unit, has been proved to be a multitalented synthetic building block with its high density of functional groups with donor and acceptor reactivity. It can be used in domino reactions comprising imine additions and intramolecular acylations, which lead in one-pot reactions with **1** to dihydropyrrolones, bisdihydropyrrolones, and spiro[pyrrolinone-3,3′-dihydropyrrolinones]. Furthermore, tricyclic spiro compounds become available using simple reaction conditions.

Experimental Section[19]

3/4: Compound **1** (0.5 g, 2.3 mmol) was dissolved in methanol (5 mL) and after addition of imine (2.3 – 3.5 mmol) the solution was stirred at room temperature for three days. Subsequently the solvent was removed on a rotary evaporator and **3/4** was isolated from the crude product by flash chromatography (petroleum ether/diethyl ether 1/1 (*v*/*v*)).

5a: Compound **1** (2.3 mmol) was dissolved in methanol (5.0 mL) in a 25 mL flask (closed with a fermentation tube filled with paraffin oil). After addition of **2a** (2.3 mmol) and benzylamine (2.3 mmol), the solution was stirred for five days at room temperature. The resulting white precipitate was collected and washed with methanol.

5b, c: Compound **1** (2.3 mmol) and imine (3.5 mmol) were dissolved in methanol (50 mL) in a 250 mL flask (closed with a fermentation tube filled with paraffin oil), stirred for three days at room temperature, and left to stand for 12 weeks. The yellow or white crystals, respectively, were collected and washed with methanol.

6a, **d**: Compound **1** (0.5 g, 2.3 mmol) and imine (4.6 mmol) were dissolved in *m*-xylene (10 mL) and heated for 15 h under reflux. Subsequently the solvent was removed on a rotary evaporator and the residue dissolved in methanol (5 mL). The precipitate, which formed after three days at − 20 °C, was collected and washed with methanol.

6b, c, **e**, **f**: Compound **1** (0.5 g, 2.3 mmol) and imine (4.6 mmol) were stirred without solvent at 70 °C for 48 h and the product was isolated by either flash chromatography or recrystallization from methanol.

7b, c: Compound **1** (0.5 g, 2.3 mmol) and imine (6.9 mmol) were stirred without solvent at 70 °C for 48 h. The resulting dark red or black solid, respectively, was recrystallized from a small volume of methanol.

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[3] Trimethyl aconitate was converted with dienes to Diels – Alder cycloadducts in 50 – 95 % yield (e.g. cyclopentadiene (toluene, 120 °C) 95 %, cyclohexadiene 50 %, *trans,trans*-1,4-diphenylbutadiene 95 %).[2b]
[4] Reaction of trimethyl aconitate with aromatic and aliphatic aldehydes afforded Knoevenagel condensates in 36 – 93 % yield (e.g. benzaldehyde (toluene, piperidinium acetate, reflux) 56 %, *p*-methoxybenzaldehyde 93 %, cyclohexanecarbaldehyde 60 %).[2b]
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[14] When **1** and *N*-benzylidene-*N*-ethylamine were allowed to react at room temperature, the reaction stopped at the imine adduct (R^1: phenyl, R^2: ethyl), which was isolated as one diastereomer in 39 % yield without undergoing the second intramolecular acylation.
[15] To our knowledge no synthesis has been reported to date for the substituted spiro[pyrrolidinone-3,3-dihydropyrrolinone] framework. For an elegant spiro[pyrrolidinone-3,3′-oxindole] synthesis see reference [16a] and references therein. For a spiro[succinimide-3,3′-oxindole] synthesis see reference [16b]. For spiro[pyrrolidinone-3,3′-pyrrolidinone] syntheses starting from dialkyl malonates see reference [16c].
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[18] The crystal structures of the main diastereomers of **6a** and **6b** have the (5*S**, 6*R**) configuration at the two stereogenic centers.
[19] Crystal structures of the compounds **3a**, **4e**, **5a** – **c**, **6a**, **6d**, **7a** – **c** have been obtained. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos CCDC-163546 (**7c**), CCDC-163547 (**5a**), CCDC-169695 (**3a**), CCDC-169696 (**4e**), CCDC-169697 (**5b**), CCDC-169698 (**5c**), CCDC-169699 (**6a**), CCDC-169700 (**6d**), CCDC-169701 (**7a**), and CCDC-169702 (**7b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Electrophilic Fluorination Mediated by Cinchona Alkaloids: Highly Enantioselective Synthesis of α-Fluoro-α-phenylglycine Derivatives**

Barbara Mohar, Jérôme Baudoux, Jean-Christophe Plaquevent, and Dominique Cahard*

The discovery of efficient methods for asymmetric fluorination is one of the most fascinating aspects of modern organofluorine chemistry.[1] Indeed, molecules bearing a stereogenic fluorinated carbon atom are of great interest in bio- and medicinal chemistry research. For example, fluorinated amino acids are of special interest for the design of new fluorine-containing peptides with unusual folding patterns, due to H···F bonding, which show interesting biological properties.[2] However, there are to date no reports on the enantioselective synthesis of α-fluoro-α-amino acids.[3]

We recently developed a fundamentally new class of enantioselective electrophilic fluorinating reagents (noted hereafter $[N-F]^+$) derived from cinchona alkaloids.[4] Independently, Shibata and co-workers reported a conceptually similar approach,[5] in which the chiral fluorinating agent was not isolated, but generated in situ. While these studies demonstrated the ability of enantioselective F^+ transfer, further work must be undertaken to reach still higher enantioselectivities. Typical substrates used in both studies were ketones and β-ketoesters for the ease of enolate formation. We report herein the first enantioselective α-fluorination of α-amino acid derivatives. We have carried out extensive studies on the relationship between the structure and enantioselectivity of $[N-F]^+$ cinchona alkaloid derivatives and have discovered that a number displayed very high enantioselectivities. Enantioselection as high as 94 % was attained, exceeding all previous records and indicating that electrophilic fluorination mediated by cinchona alkaloids is a powerful method for the construction of fluorinated chiral centers.

Our successful approach to asymmetric electrophilic fluorination was based upon reacting the preformed ester enolate or nitrile anion with modified *N*-fluoro-cinchona alkaloids. In a first set of experiments, we examined the performance of the first generation of $[N-F]^+$ reagents, namely the four naturally occurring cinchona alkaloids, which have an unprotected hydroxy function. We found that these reagents displayed poor to moderate enantioselective fluorination (7 – 48 % *ee*). We then turned our attention to the structure – enantioselectivity relationship operating in various parts of the *N*-fluoro-

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