Modulation of Reactivities of Dienophiles for *Diels–Alder* Reactions *via* Complexation of *α,β*-Unsaturated Chelating Amides

by **Markus Sterk** and **Willi Bannwarth***

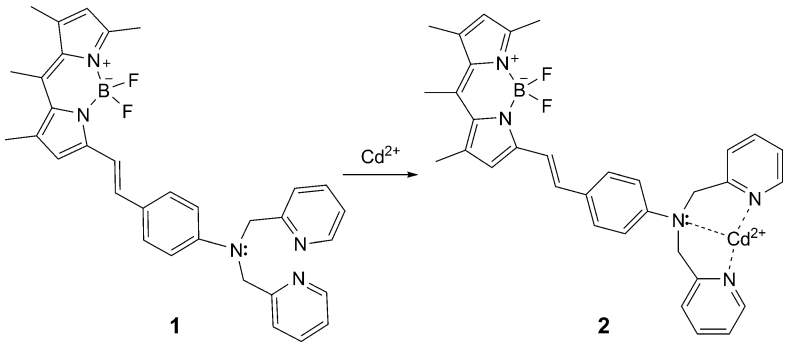
Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg, Albertstraße 21, DE-79104 Freiburg (fax: +49-761-2038705; e-mail: willi.bannwarth@organik.chemie.uni-freiburg.de)

We describe the modulation of reactivities of dienophiles for *Diels–Alder* reactions *via* a new principle based on chelating amides positioned adjacent to their C=C bond. It is demonstrated for modified acrylic acid derivatives and related dienophiles with three different chelating entities. Complexation of the chelators leads to an intensified electron-withdrawing effect leading to an enhancement of reactivity in *Diels–Alder* reactions depending on the complexed metal ion. The application of this new approach might be extended to other reactions with reacting entities adjacent to chelating amides.

Introduction. – In the last decade, the interest in applications of the chelating entity bis(pyridin-2-ylmethyl)amine (bpa; **5**) and related amides thereof has increased significantly. It was recently demonstrated that the photochemical and photophysical properties of chromophores equipped with bpa could be significantly influenced by complexation of metal ions. In *Scheme 1*, we present an example where the complexation of the boron-dipyrromethane (BODIPY; 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dye **1** with Cd^{2+} led to an electron-withdrawing effect in **2**, influencing the π-conjugated backbone of the molecule and hence its fluorescence properties. Thus, the complexation of the Cd^{2+} resulted in a blue shift of the fluorescence emission from 656 to 597 nm [1].

Further examples of the electron-withdrawing effect caused by complexation of bpa are shown in *Fig. 1*, and they range from modulation of the luminescence by Zn^{2+} ions

Scheme 1. *Example of the Complexation of bpa-Containing Chromophore* **1** *Used as a Selective Fluorescent Sensor*



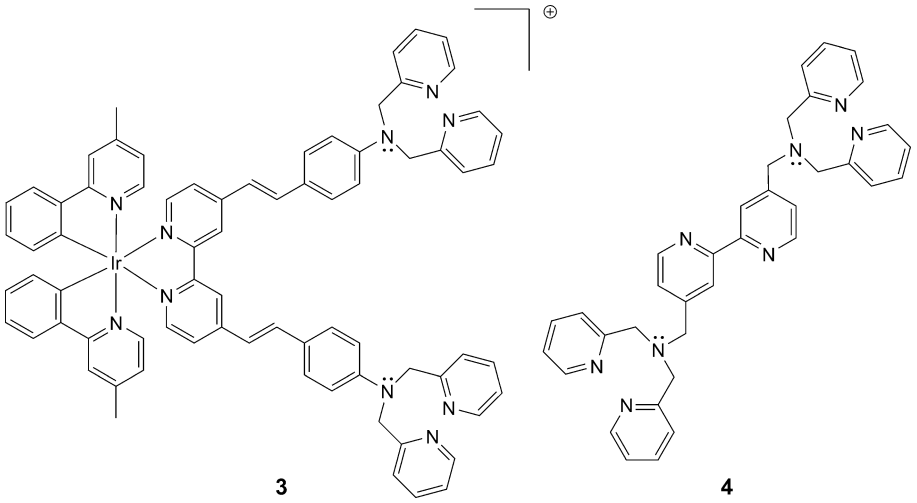


Fig. 1. *bpa-Containing complex* **3** *and chelating ligand* **4**

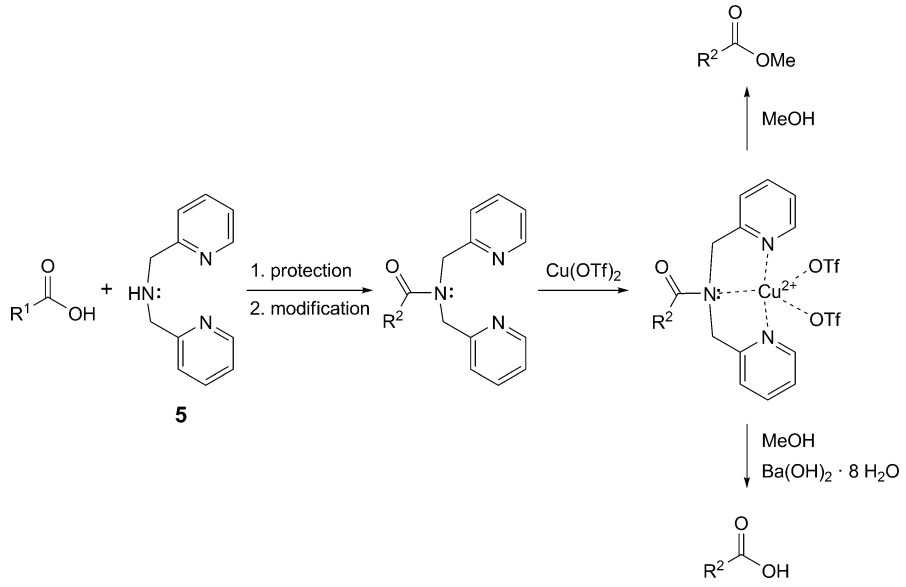
in Ir complex **3** to detection of protein-coupled phosphates *via* coordination to Zn^{2+}, complexed by bpa-containing chromophores [2][3]. Besides these photochemical applications, alterations of affinities for intercomponent H-bonds of bpa-modified amides due to complexation of Cd^{2+} were described as well [4].

bpa Derivatives were also used to modulate catalyst reactivities, such as those of metal-complexes with **4**, which showed increasing catalytic activity in hydrolysis reactions due to a metal ion-induced allosteric transition [5].

The influence of chelating systems on chemical reactivities was already demonstrated in 1970. It was observed that bpa amides of carboxylic acids dissolved in MeOH were prone to a conversion to the pertinent methyl esters after complexation to Cu^{2+} [6]. The synthetic potential of this seminal observation had not been recognized, until our group has used these intriguing features to develop two different linker units for solid-phase chemistry and to establish a novel relay protection scheme for carboxylic acids as outlined in *Scheme 2* [7–9].

The protection can easily be performed by standard amide couplings by employing the carboxylic acid, bpa (**5**), and an activation agent. The resulting amide is chemically very robust, and hence it is highly inert towards different reaction conditions, allowing for a wide array of chemical operations on the adjacent residue to be performed. Yet, its deprotection can be achieved under very mild conditions and proceeds in an orthogonal fashion compared to most commonly employed protecting groups for carboxylic acids. Disadvantages due to use of $Cu(OTf)_2$ could be solved by selecting amine **6** (*Fig. 2*) as an alternative for bpa (**5**) [10]. It showed the same general features as described for the protection with bpa, but the deprotection of the pertinent amide was significantly faster by applying $CuCl_2$. In addition, we had synthesized the structurally related ligand **7** (*Fig. 2*), which was similar to ligand **6** but carried an additional coordinating N-atom.

Scheme 2. *Principle of the bpa-Based Relay Protection of Carboxylic Acids*



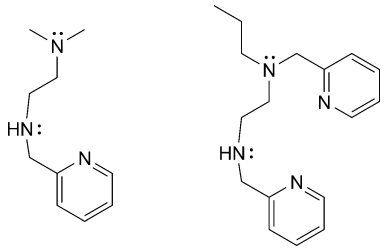


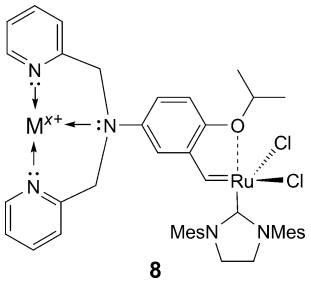
Fig. 2. *Structures of chelating ligands* **6** *and* **7**

In a simultaneous application of carboxylic acid amides, which were modified with the three chelating entities **5**–**7**, it was even possible to cleave one chelating unit after the other in an orthogonal fashion by employing different metal salts [11].

At this point, we surmised that complexation of chelating entities and the resulting electron-withdrawing effect might open up a general strategy for the modulation of reactivities or the induction of a reaction. Along these lines, this was first probed for the *Hoveyda*-type catalysts of type **8**.

We were able to demonstrate that a complexation of the chelating unit in catalyst **8** (*Fig. 3*) had a significant positive effect on its efficiency in metathesis reactions [12].

Herein, we report on an application of this new principle on *Diels–Alder* reactions of acrylic acid amides and related derivatives as dienophiles. Such reactions of electron-poor dienophiles with electron-rich dienes (normal electron demand) are governed by



8

Fig. 3. Hoveyda-*type catalyst* **8**

the energy gap between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile [13][14]. This gap can be lowered by factors increasing the electron density on the diene or decreasing that on the dienophile. A common strategy to achieve the latter is the addition of *Lewis* acids acting on the amide's O-atom [15]. We assumed that an inhibition of the amide resonance by complexation, as illustrated in *Fig. 4*, should result in the same effect. To the best of our knowledge, this would represent a novel and innovative approach to modulate reactivities of dienophiles in *Diels–Alder* reactions and might have implications for other reactions as well.

The strategy would allow us to employ different but related dienophiles (R = H, COOEt, $CONEt_2$) in combination with our three different chelating units (**5**, **6**, and **7**) with and without complexation. It would also enable comparison of earlier results on the influence of different metal ions on the methanolysis of the pertinent amides with the reactivity in *Diels–Alder* reactions.

An additional interesting aspect would concern the influence of the complexation on secondary orbital interactions governing the *endo*/*exo* ratio of the cycloadduct.

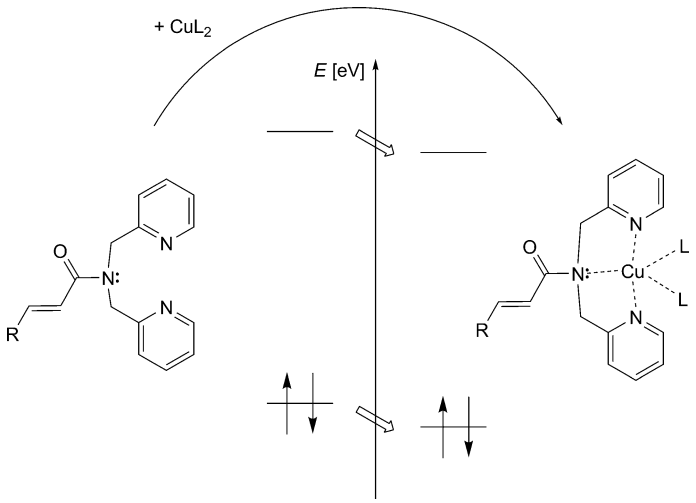
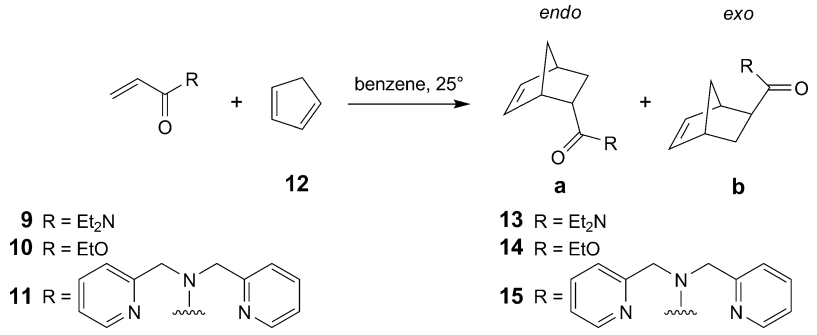


Fig. 4. *Effect of the complexation on the frontier orbitals of the dienophile*

Results and Discussion. – As a first step we performed *Diels–Alder* reactions as outlined in *Scheme 3* with acrylic acid (prop-2-enoic acid) derivatives **9**–**11** as dienophiles and cyclopentadiene without or after addition of stoichiometric amounts of a Cu^{2+}-ion source [16].

The results of these studies are outlined in *Fig. 5*. For each case, the curves indicate the combined formation of the *endo*- and the *exo*-cycloadduct as a function of the

Scheme 3. Diels–Alder *Reactions of Some Acrylic Acid Derivatives without or in the Presence of* $Cu(OTf)_2$ *Using 4.0 equiv. of Cyclopenta-1,3-diene* (**12**)



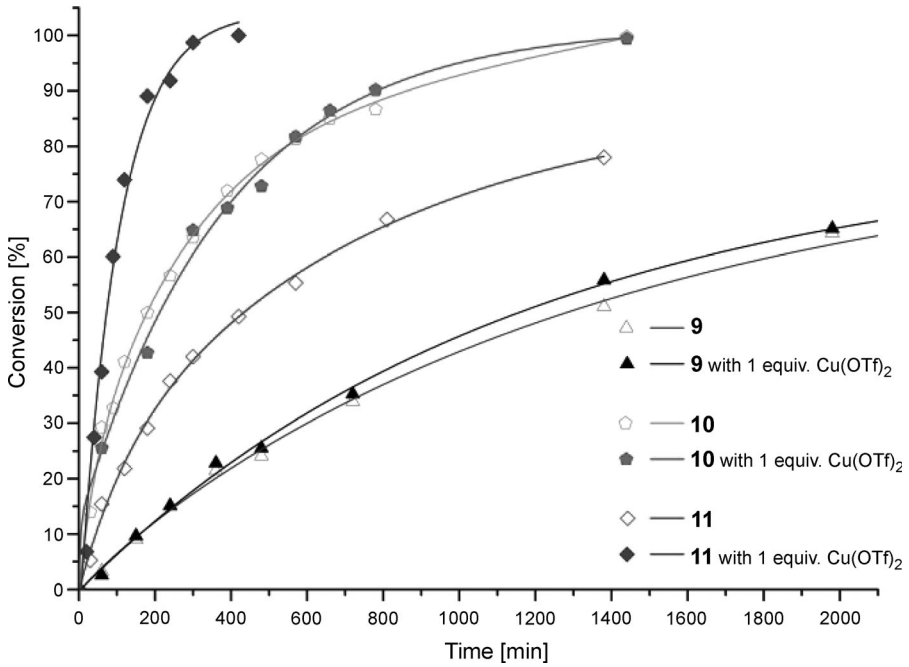


Fig. 5. Diels–Alder *reactions of* **9**–**11** *with cyclopenta-1,3-diene* (**12**) *without and after addition of* $Cu(OTf)_2$

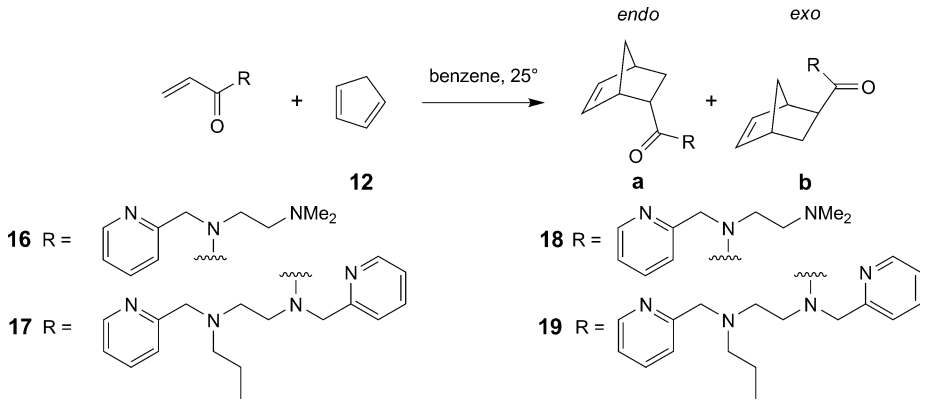
reaction time. The reaction of dienophile **9** served as a benchmark reaction due to its inability to complex Cu^{2+}, and hence its addition had no influence on the reactivity. The ester dienophile **10** showed a significantly enhanced reaction rate, caused by the much lower resonance energy of esters compared to amides, and its reactivity was not influenced by the addition of an equimolar amount of $Cu(OTf)_2$. In contrast, coordination of chelating unit of **11** to an equimolar amount of $Cu(OTf)_2$ revealed, to our delight, a significant enhancement of the reactivity, even surmounting that of the ester dienophile **10**.

Besides the use of $Cu(OTf)_2$, we evaluated the impact of various metal salts all of which had shown an influence on the methanolysis rate of bpa-modified amides in earlier studies [11]. Surprisingly, other Cu sources such as CuCl and $CuCl_2$ had no influence on the reactivity. Hence, the effect can be regarded as $Cu(OTf)_2$-specific, indicating at the same time that the effect of the counter ion cannot be neglected.

In addition to the acceleration of the *Diels–Alder* reaction by complexation we observed also a significant effect on the *endo*/*exo* ratio of the cycloadducts. The ratio in the uncomplexed state, 1.3 : 1, increased to 6.8 : 1 after complexation which can only be explained by an influence on secondary orbital interactions.

The aforementioned investigations concerning the bpa-amide **11** were then extended to the related chelating derivatives **16** and **17** (*Scheme 4*).

Scheme 4. Diels–Alder *Reactions of Acrylic Acid Derivatives* **16** *and* **17** *Using 4.0 Equiv. of Cyclopenta-1,3-diene* (**12**)



Addition of $Cu(OTf)_2$ to **16** led only to a slight enhancement of reactivity and an alteration of the *endo*/*exo* rate from 1.5 : 1 to 4.5 : 1. In contrast, addition of CuCl resulted in a pronounced acceleration of the cycloaddition (*Fig. 6*) but without change of the *endo*/*exo* ratio. As opposed to these results, the addition of Cu salts to amide **17** carrying the tetradentate entity had only a moderate effect. The most significant effect was observed with $Zn(OTf)_2$ (*Fig. 6*), and the *endo*/*exo* ratio increased from 1.6 : 1 to 9.5.1.

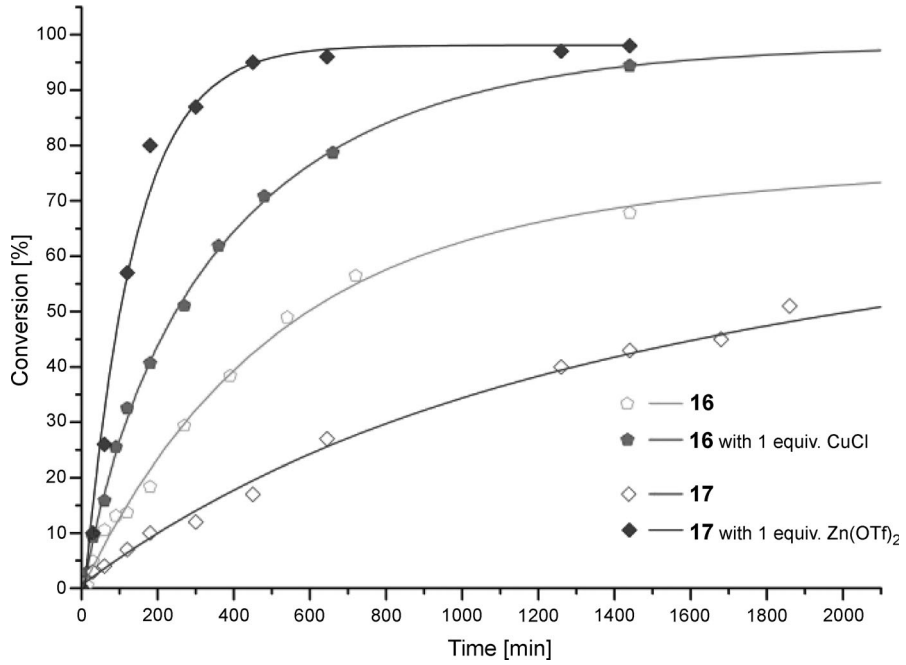


Fig. 6. Diels–Alder *reactions of* **16** *before and after addition of CuCl and* **17** *before and after addition of* $Zn(OTf)_2$ *with cyclopenta-1,3-diene* (**12**)

After having established that the bpa-modified acrylamide **11** was most influenced by the addition of $Cu(OTf)_2$, and that CuCl had the highest impact on the dmepa-amide **16**, and $Zn(OTf)_2$ had led to the highest acceleration of the tetradentate-amide **17**, we expanded our investigations to the corresponding fumaric amides ((2*E*)-but-2-enediamides) **20**–**22** and **23**–**25**, as outlined in *Scheme 5*.

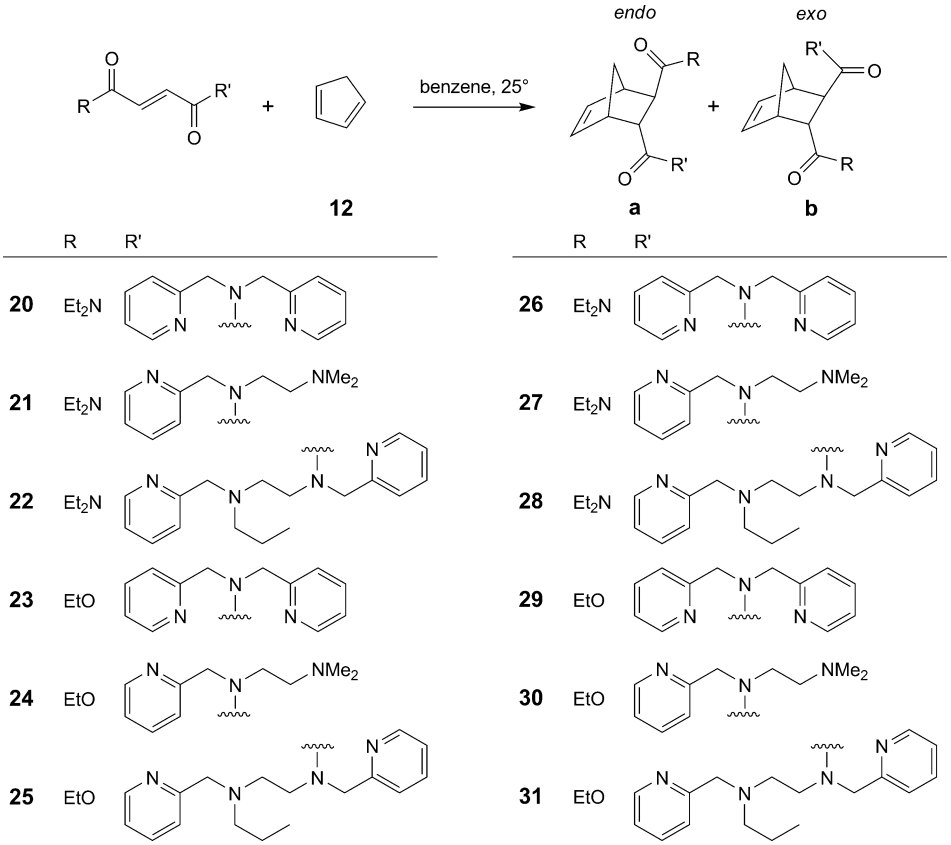
Compared to the acrylamides **11**, **16** and **17**, we expected a higher benchmark reactivity of these amides in the uncomplexed form due to the additional amide or ester function, respectively. Hence, it was interesting to see whether an influence on the activities by complexation was still observable.

According to the results obtained with the acrylamides, compounds **20** and **23** were tested before and after the addition of $Cu(OTf)_2$, whereas amides **21** and **24** were complexed with CuCl. Finally, amides **22** and **25** were investigated before and after complexation with $Zn(OTf)_2$. The results are compiled in *Figs. 7* and *8*.

As can be deduced from *Fig. 7*, the complexation resulted again in a significant enhancement of the reaction despite of the higher benchmark reaction rates of the uncomplexed dienophiles. In contrast to the results with the acrylamides, no distinct change in the *endo*/*exo* selectivity was observed.

Similar results were obtained for the even more reactive derivatives **23**–**25** before and after complexation (*Fig. 8*), demonstrating at the same time a slight influence on the *endo*/*exo* ratios (see *Exper. Part*).

Scheme 5. Diels–Alder *Reactions of the Fumaric Acid Derivatives* **20**–**25**



Conclusions. – In summary, we were able to verify as a new principle that *Diels–Alder* reactions of chelating ligand-modified dienophiles could indeed be accelerated by addition of metal salts, thereby indicating that the resulting complexes are affecting frontier orbitals of these modified dienophiles and, in some cases, also the secondary orbital interactions. Reactivity enhancements of bpa-modified dienophiles **11**, **20**, and **23** can be regarded as nearly selective for $Cu(OTf)_2$ and an influence on the *endo*/*exo* ratios could be observed as well. In contrast, mixed tridentate-modified dienophiles, **16**, **21**, and **24**, showed the most pronounced acceleration with CuCl, without influencing the *endo*/*exo* selectivity. Addition of $Zn(OTf)_2$ to the *Diels–Alder* reaction of tetradentate-modified dienophiles **17**, **22**, and **25** resulted in a significant enhancement of reactivity as well as a moderate effect on the *endo*/*exo* selectivities. The described results offer an elegant possibility of modulating reactivities of *Diels–Alder* reactions with α,β-unsaturated chelating amides. The principle might be more generally applicable to activate reacting entities in the neighborhood of chelating amides. For these reasons, we assume that the presented data could be of more general interest.

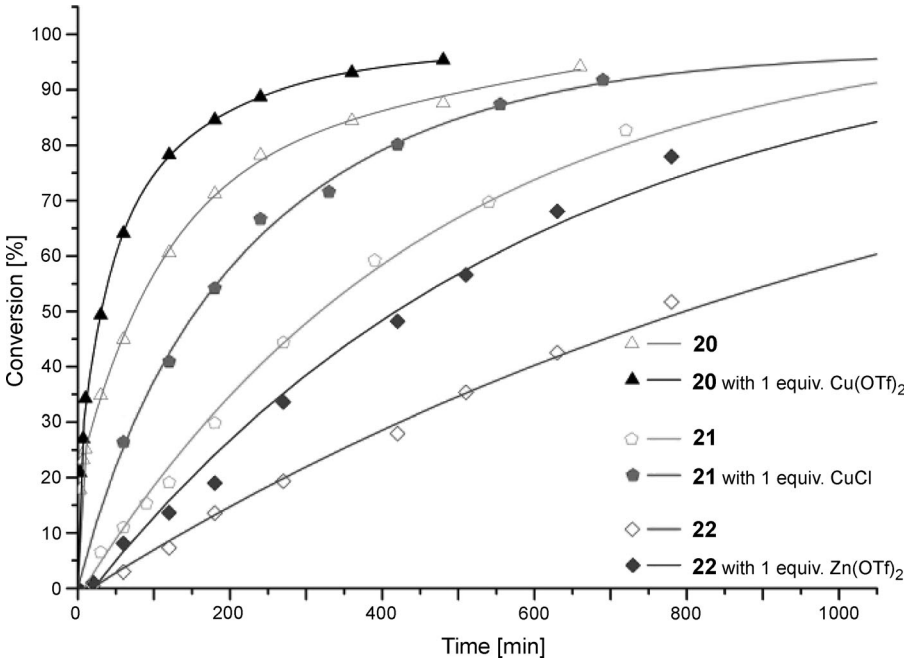


Fig. 7. Diels–Alder *reactions of* **20**–**22** *before and after complexation*

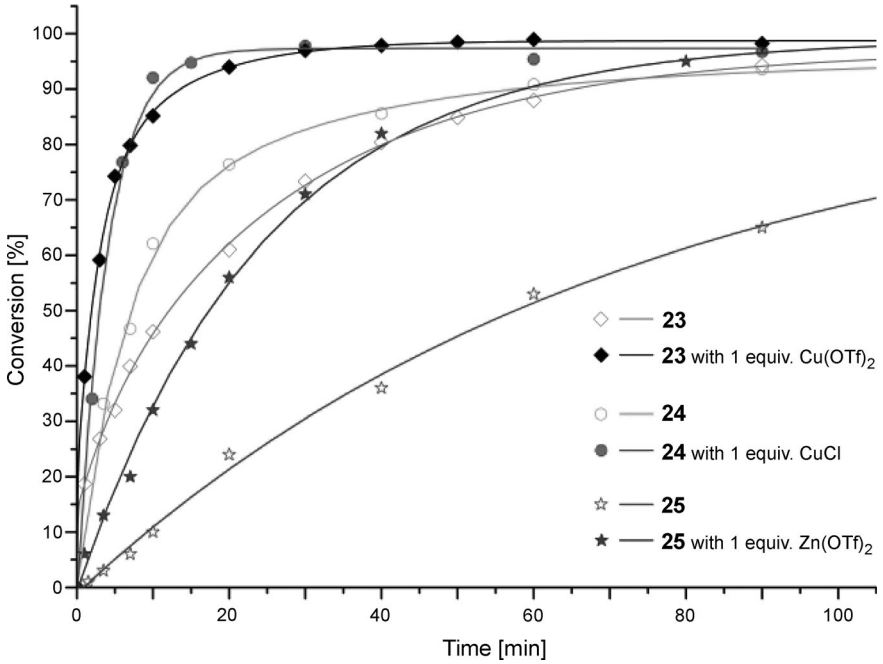


Fig. 8. Diels–Alder *reactions of* **23**–**25** *before and after complexation*

Experimental Part

General. All reactions with air- and moisture-sensitive compounds were carried out under Ar. All solvents were of anal. grade or better.

The *Diels–Alder* reactions carried out in 1.5-ml *Eppendorf* tubes; evaporations in a *Hettlab IR-Dancer*.

Column chromatography (CC): *Merck* silica gel *60* (40–63 μm) or *Machery–Nagel* basic aluminium oxide (activity 1); solvents, *i.e.*, CH_2Cl_2, cyclohexane, AcOEt, EtOH, freshly distilled or of p.a. quality (MeOH); the progress of the reactions checked by TLC (silica gel *60*, *F-254*, *Merck*); and detection under UV light (254 nm) or after staining with aq. $KMnO_4$-soln. HPLC: *Agilent 1100* series HPLC system or *MERCK-HITACHI* system, containing the following components: *L-5025* column thermostat, *L-4400* Diode array detector, *L-6200A* intelligent pump, *AS-2000A* autosampler, and *D-6000* interface; columns, solvents, and the flow rates depending on the *Diels–Alder* reaction; all solvents filtered before being used for the measurements. Used columns were: *Daicel Chiralpak* (0.4 cm × 25 cm with *ADH* couting and *ADH* precolumn), *Daicel Chiralpak* (0.4 cm × 25 cm with *ODH* couting and *ODH* precolumn), *Waters X-Terra* RP_{18} (5 μm 4.6 mm × 250 mm), and *LiChrosphor LiChroCART 250-4 Si 60* (5 μm). ^{1}H-NMR Spectra (first order): *Bruker AM 400* (400 MHz) or a *Varian Mercury VX 300* (300 MHz) spectrometers; in $CDCl_3$; chemical shifts (δ) in ppm with reference to TMS ($\delta = 0.00$ ppm) and to $CHCl_3$ (7.26 ppm) as internal standards; coupling constants (J) as absolute values. ^{13}C-NMR Spectra: *Bruker AM 400* (100 MHz) or a *Bruker Avance DRX* (125 MHz) spectrometer; in $CDCl_3$. chemical shifts (δ) in ppm with reference to TMS ($\delta = 0.00$ ppm) and to $CHCl_3$ (77.2 ppm, t) as internal standards. MS: *Finnigan MAT312* and *TSQ 700* spectrometers by using electron impact (EI), chemical ionization (CI), and GC/MS (EI or CI); additionally, electrospray ionization mass spectrometry (ESI) and atmospheric-pressure chemical-ionization (APCI) mass spectra recorded with a *LCQ Advantage* or *Exactive*. HR-MS: *Thermo Exactive* with orbitrap-analysator spectrometer; the molecular fragments quoted in m/z, the intensities as a percentage value relative to the intensity of the base signal (100%). Elemental analyses: *Elementar Vario EL* (*Elementar Analysesysteme GmbH*).

General Procedure for Acylation of Various Amines Using TBTU (*GP 1*). The carboxylic acid (1.5 equiv.) and TBTU (*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; 1.5 equiv.) were suspended in the chosen solvent (either DMF or CH_2Cl_2) [17]. $EtN(^iPr)_2$ (6.0 equiv.) was added, and the mixture was stirred for 20 min. After addition of amine **5**, **6** or **7** (1.0 equiv.) and stirring overnight at r.t., the mixture was washed with sat. aq. $NaHCO_3$ soln. and H_2O, and dried (Na_2SO_4). The org. solvent was evaporated, and the crude product was purified *via* flash chromatography (FC; SiO_2; CH_2Cl_2/MeOH 99 : 1 → 85 : 15).

General Procedure for Diels–Alder *Reactions with Cyclopentadiene* (**12**) *without Metal Salts* (*GP 2*). The dienophile (1.0 equiv.) was dissolved in benzene and after addition of freshly cracked and distilled **12** (4.0 equiv.), the mixture was stirred at r.t. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ soln. and H_2O. After drying (Na_2SO_4), the org. solvent was evaporated, and the crude product was purified by FC (SiO_2; CH_2Cl_2/MeOH 99 : 1 → 85 : 15).

General Procedure for Diels–Alder *Reactions with* **12** *and Cu(OTf)$_2$* (*GP 3*). The dienophile (1.0 equiv.) was dissolved in benzene, mixed with $Cu(OTf)_2$ (1.1 equiv.), and stirred for 30 min to obtain the Cu^{2+} complex. After addition of freshly cracked and dist. **12** (4.0 equiv.), the mixture was stirred at r.t., and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with KCN soln. (0.5M) and H_2O (2 ×). After drying (Na_2SO_4), the org. solvent was evaporated, and the crude product purified by FC (SiO_2).

General Procedure for the Kinetic Studies of Diels–Alder *Reactions with* **12** (*GP 4*). The dienophile (1.0 equiv.) was dissolved in benzene in a 1.5-ml *Eppendorf* tube and mixed with the appropriate salt (1.0 equiv.), in the case of metal addition. After shaking for 30 min at 25° with 850 rpm, freshly cracked and dist. **12** (4.0 equiv.) was added, and the mixture was shaken at 25° (850 rpm). Samples for HPLC were prepared by taking 10 μl of the soln. and addition of heptane (0.5 ml). The org. phase was washed with KCN soln. (0.5M) and H_2O (2 ×). The org. phase was used for HPLC.

General Procedure for the Kinetic Studies of the Diels–Alder *Reactions with* **12** (*GP 5*): The dienophile (1.0 equiv.) was dissolved in benzene in a 1.5-ml *Eppendorf* tube and mixed, in the case of

metal addition, with the appropriate salt (1.0 equiv.). After shaking for 30 min at 25° (850 rpm), freshly cracked and dist. **12** (4.0 equiv.) was added, and the mixture was stirred at 25° (850 rpm). Samples for HPLC were prepared by taking 10 µl of the soln. After evaporation under reduced pressure *IR Dancer*, the residue was dissolved in Et_2O and washed with KCN soln. (0.5M) and H_2O (2×). The org. solvent was evaporated using an *IR Dancer*, and the crude mixture was dissolved in an adequate HPLC solvent.

N,N-*Bis(pyridin-2-ylmethyl)prop-2-enamide* (**11**). Compound **11** was synthesized according to *GP 1* by using acrylic acid (0.25 g, 3.75 mmol, 1.5 equiv.) and *1-(pyridin-2-yl)-N-(pyridin-2-ylmethyl)methanamine* (**5**; 0.50 g, 2.50 mol, 1.0 equiv.) in DMF. The resulting dark oil was purified by CC (SiO_2; CH_2Cl_2/MeOH 99:1 → 90:10) to yield **11** (0.49 g, 1.94 mmol, 78%). Brown oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): 4.80 (*s*, CH_2N); 4.85 (*s*, CH_2N); 5.71 (*dd*, *J* = 10.5, 2.0, 1 H, CH=CH_2); 6.45 (*dd*, *J* = 16.8, 2.0, 1 H, CH=CH_2); 6.65 (*dd*, *J* = 16.8, 10.4, C*H*=CH$_2$); 7.15–7.21 (*m*, 3 arom. H); 7.36–7.40 (*m*, 1 arom. H); 7.62–7.68 (*m*, 2 arom. H); 8.49–8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 51.9; 53.2; 120.9; 122.5; 122.6; 122.8; 127.7; 129.2; 136.9; 137.0; 149.3; 150.0; 156.9; 157.3; 167.3. ESI-MS (pos.): 254.1 (100, $[M + H]^+$). HR-APCI-MS (pos.): 254.1290 ($[M+H]^+$, $C_{15}H_{16}N_3O^+$; calc. 254.1293).

N,N-*Diethylbicyclo[2.2.1]hept-5-ene-2-carboxamide* (**13**). A mixture of **13a** and **13b** was synthesized according to *GP 2*, by using N,N-*diethylprop-2-enamide* (**9**; 0.50 g, 3.90 mmol, 1.0 equiv.), and freshly cracked and dist. **12** (1.30 ml, 15.7 mmol, 4.0 equiv.). After 5 d, and removal of solvent and remaining **12** under reduced pressure, the crude product was purified by CC (SiO_2; cyclohexane/AcOEt 98:2) to yield **13a** (0.30 g, 1.55 mmol, 40%) and **13b** (0.18 g, 0.93 mmol, 24%). Colorless oils.

Data of **13a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.11 (*t*, *J* = 7.1, *Me*CH_2); 1.20 (*t*, *J* = 7.1, *Me*CH_2); 1.34–1.40 (*m*, 1 H of CH_2(7)); 1.75–1.79 (*m*, 1 H, CH_2(7)); 1.80–1.86 (*m*, 1 H, CH_2(3)); 2.25–2.30 (*m*, CH); 2.89–2.92 (*m*, CH, CH(2)); 3.31–3.42 (*m*, 2 MeCH_2); 6.12–6.17 (*m*, CH=CH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.1; 14.5; 31.5; 40.1; 40.7; 41.6; 41.7; 46.6; 46.9; 136.4; 138.3; 174.9.

Data of **13b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.07 (*t*, *J* = 7.1, *Me*CH_2); 1.16 (*t*, *J* = 7.14, *Me*CH_2); 1.28–1.31 (*m*, 1 H, CH_2(7)); 1.39–1.46 (*m*, 1 H of CH_2(7), 1 H of CH_2(3)); 1.88–1.95 (*m*, 1 H, CH_2(3)); 2.87–2.91 (*m*, CH); 2.99–3.03 (*m*, CH(2)); 3.06–3.09 (*m*, CH); 3.17–3.53 (*m*, 2 MeCH_2); 6.02 (*dd*, *J* = 5.6, 3.0, C*H*=CH); 6.17 (*dd*, *J* = 5.6, 3.0, C*H*=CH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.0; 14.5; 31.2; 39.8; 41.1; 41.8; 42.8; 46.1; 49.7; 132.8; 136.4; 173.2. APCI-MS (pos.): 194.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 194.1546 ($[M+H]^+$, $C_{12}H_{20}NO^+$; calc. 194.1545).

Conversion from dienophile **9** to the mixture **13a**/**13b** was monitored *via GP 4*. HPLC was performed with an achiral *Si60* column (*LiChroCHART 250-4*) with heptane/^{i}PrOH 4:1, a flow rate of 0.5 ml/min and detection at 210 nm, resulting in the following retention times (t_R: 8.3 (**13a**), 9.3 (**13b**), and 13.7 (**9**) min.

Ethyl Bicyclo[2.2.1]hept-5-ene-2-carboxylate (**14**). A mixture **14a**/**14b** was synthesized according to *GP 2*, by using *ethyl prop-2-enoate* (**10**; 0.25 g, 2.50 mmol, 1.0 equiv.) and freshly cracked and dist. **12** (0.83 ml, 10.0 mmol, 4.0 equiv.). After 30 h, and removal of solvent and remaining **12** under reduced pressure, the crude product was purified by CC (SiO_2; cyclohexane/AcOEt 9:1 → 1.5:1) to yield **14a**/**14b** (0.38 g, 2.30 mmol, 94%; *endo*/*exo* 3:1). Colorless oil.

Data of **14a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.24 (*t*, *J* = 7.3, *Me*CH_2); 1.25–1.29 (1 H, CH_2(7)); 1.40–1.45 (*m*, 1 H of CH_2(7), 1 H of CH_2(3)); 1.86–1.95 (*m*); 2.88–2.96 (*m*, CH, CH(2)); 3.19–3.22 (*m*, CH); 4.03–4.12 (*m*, MeCH_2); 5.93 (*dd*, *J* = 5.6, 2.8, C*H*=CH); 6.19 (*dd*, *J* = 5.7, 3.0, C*H*=CH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.4; 29.3; 42.7; 43.5; 45.8; 49.7; 60.2; 132.5; 137.8; 174.8.

Data of **14b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.26 (*t*, *J* = 7.2, *Me*CH_2); 1.26–1.39 (*m*, 1 H of CH_2(7), 1 H of CH_2(3)); 1.51–1.56 (*m*, 1 H, CH_2(7)); 1.86–1.95 (*m*, 1 H, CH_2(3)); 2.18–2.24 (*m*, CH(2)); 2.88–2.96 (*m*, CH); 3.02–3.05 (*m*, CH); 4.10–4.18 (*m*, MeCH_2); 5.93 (*dd*, *J* = 5.6, 2.9, C*H*=CH); 6.14 (*dd*, *J* = 5.6, 2.8, C*H*=CH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.4; 30.4; 41.7; 43.3; 46.4; 46.7; 60.4; 135.9; 138.1; 176.3. APCI-MS (pos.): 167.1 (100, $[M + H]^+$). HR-APCI-MS (pos.): 167.1072 ($[M+H]^+$, $C_{10}H_{15}O_2^+$; calc. 167.1072).

Conversion of dienophile **10** to the mixture **14a**/**14b** was monitored *via GP 4*. HPLC was performed with a achiral *Si60*-column (*LiChroCHART 250-4*) with heptane/^{i}PrOH 95:5; a flow rate of 0.5 ml/min and detection at 210 nm resulting in the following t_R values: 7.7 (**14b**), 9.2 (**14a**), and 10.4 (**10**) min.

N,N-*Bis(pyridin-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide* (**15**). A mixture **15a**/**15b** was synthesized according to *GP 3* by using N,N-*bis(pyridin-2-ylmethyl)prop-2-enamide* (**11**; 39.5 mg,

0.16 mmol, 1.0 equiv.), $Cu(OTf)_2$ (57.8 mg, 0.16 mmol, 1.0 equiv.), and freshly cracked and dist. **12** (51.5 µl, 0.62 mmol, 4.0 equiv.). After 16 h, the solvent and remaining **12** were removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (25 ml), washed with sat. aq. $NaHCO_3$ soln. (25 ml), and H_2O (25 ml) and the org. phase was dried (Na_2SO_4). The solvent was removed under reduced pressure. Purification by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) afforded **15a**/**15b** (48.2 mg, 0.15 mmol, 97%; *endo*/*exo* 1.3 : 1). Slightly brown gum.

Data of **15a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.22 – 1.27 (*m*, 1 H, CH_2(7)); 1.40 (*ddd*, *J* = 8.3, 4.5, 1.9, 1 H, CH_2(7)); 1.52 (*ddd*, *J* = 11.3, 4.6, 2.6, 1 H, CH_2(3)); 1.90 (*ddd*, *J* = 11.3, 9.3, 3.8, 1 H, CH_2(3)); 2.87 – 2.91 (*m*, CH); 3.09 – 3.12 (*m*, CH); 3.19 (*ddd*, *J* = 9.2, 4.6, 3.2, CH(2)); 4.56 – 4.96 (*m*, 2 CH_2N); 6.03 (*dd*, *J* = 5.6, 2.9, C*H*=CH); 6.22 (*dd*, *J* = 5.6, 3.0, C*H*=CH); 7.12 – 7.25 (*m*, 4 arom. H); 7.60 – 7.71 (*m*, 2 arom. H); 8.47 – 8.59 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 31.0; 41.7; 42.9; 46.3; 49.8; 51.4; 52.8; 120.7; 122.2; 122.3; 122.5; 132.5; 136.8; 137.0 (2×); 149.2; 150.0; 157.4; 157.8; 175.2.

Data of **15b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.31 – 1.35 (*m*, 1 H, CH_2(7)); 1.36 – 1.42 (*m*, 1 H, CH_2(3); 1.77 – 1.81 (*m*, 1 H, CH_2(7)); 1.86 – 1.95 (*m*, 1 H, CH_2(3)); 2.41 – 2.45 (*m*, CH(2)); 2.87 – 2.93 (*m*, CH); 2.97 – 3.00 (*m*, CH); 4.56 – 4.96 (*m*, 2 CH_2N); 6.05 (*dd*, *J* = 5.6, 3.2, C*H*=CH); 6.11 (*dd*, *J* = 5.6, 3.0, C*H*=CH); 7.11 – 7.30 (*m*, 4 arom. H); 7.60 – 7.71 (*m*, 2 arom. H); 8.47 – 8.59 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 31.5; 40.9; 41.8; 46.6; 46.9; 51.5; 53.0; 120.7; 122.2; 122.3; 122.5; 132.5; 136.1; 136.7; 138.3; 149.2; 149.9; 157.2; 157.8; 176.8. APCI-MS (pos.): 320.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 320.1763 ($[M + H]^+$, $C_{20}H_{22}N_3O^+$; calc. 320.1763).

Conversion of dienophile **11** to **15a**/**15b** was monitored *via GP 5*. HPLC was performed with a chiral *ODH*-column (25 cm) with heptane/^{i}PrOH/EtOH 380 : 19 : 1, a flow rate of 1.0 ml/min, and detection at 210 nm, resulting in the following t_R values: 27.3 (**15b**), 30.9 + 34.9 (**15a**), and 42.7 (**11**) min. Separation of **15a** was possible, using chiral *ODH* column. For reaction times for full conversion with and without 1.0 equiv. of chosen metal-salts and *endo*/*exo* ratios, see *Table 1*.

Table 1

11 → **15**	*endo*/*exo*	Time [min]
without	1.3 : 1	3000
$Cu(OTf)_2$	6.8 : 1	250
$CuCl_2$	1.9 : 1	> 3000
CuCl	1.6 : 1	> 3000
$FeCl_3$	3.5 : 1	> 3000
$Zn(OTf)_2$	4.6 : 1	800

N-*[2-(Dimethylamino)ethyl]*-N-*(pyridin-2-ylmethyl)prop-2-enamide* (**16**). A soln. of N,N-*dimethyl*-N′-*(pyridin-2-ylmethyl)ethane-1,2-diamine* (**6**; 0.40 g, 2.20 mmol, 1.0 equiv.) in CH_2Cl_2 (20 ml) was cooled to 0° and freshly distilled acryloyl chloride (= prop-2-enoyl chloride; 0.62 g, 6.60 mmol, 3.0 equiv.) was added in one portion. After stirring at 0° for 1 h, the soln. was warmed up to r.t., and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 ml), and the org. soln. was washed with a sat. aq. soln. of $NaHCO_3$ (20 ml), and H_2O (2 × 20 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting oil was purified by CC (basic aluminium oxide, CH_2Cl_2/MeOH 99.5 : 0.5 → 95 : 5) to yield **16** (362 mg, 1.55 mmol, 71%). Brown gum. ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.23 (*s*, Me); 2.25 (*s*, Me); 2.43 – 2.55 (*m*, CH_2NMe$_2$); 3.51 – 3.64 (*m*, NCH_2CH$_2$); 4.76 – 4.80 (*m*, CH_2N); 5.62 – 5.77 (*m*, 1 H, CH=CH_2); 6.36 – 6.46 (*m*, CH=C*H*H); 6.49 – 6.71 (*m*, *H*C=CH$_2$); 7.15 – 7.34 (*m*, 2 arom. H); 7.61 – 7.71 (*m*, 1 arom. H); 8.51 – 8.60 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 45.0; 45.7; 45.8; 52.1; 57.3; 122.4; 127.4; 128.6; 136.8; 149.2; 157.5 (2×); 166.6. APCI-MS (pos.): 234.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 234.1603 ($[M + H]^+$, $C_{13}H_{20}N_3O^+$; calc. 234.1606).

N-*{2-[Propyl(pyridin-2-ylmethyl)amino]ethyl}*-N-*(pyridin-2-ylmethyl)prop-2-enamide* (**17**). Compound **17** was synthesized according to *GP 1*, by using acrylic acid (0.14 g, 2.00 mmol, 1.5 equiv.) and N-*ethyl*-N,N′-*bis(pyridin-2-ylmethyl)ethane-1,7-diamine* (**7**; 0.37 g, 1.30 mmol, 1.0 equiv.) in DMF. The

resulting black gum was purified by CC (SiO_2; CH_2Cl_2/MeOH 99:1 → 90:10) to afford **17** (0.38 g. 1.12 mmol, 86%). Dark green oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.87 (*t*, *J* = 8.2, *Me*CH_2); 1.46–1.55 (*m*, MeCH_2); 2.48 (*t*, *J* = 7.4, NCH_2CH_2N); 2.65 (*t*, *J* = 7.4, NCH_2CH_2N); 3.48–3.62 (*m*, NCH_2CH_2Me); 3.73 (*s*, pyCH_2N); 4.70 (*s*, CH_2N); 5.63 (*dd*, *J* = 10.3, 2.3, 1 H, CH=CH_2); 6.35 (*dd*, *J* = 16.7, 2.2, CH=CH_2); 6.51 (*dd*, *J* = 16.7, 10.3, CH=CH_2); 7.10–7.30 (*m*, 3 arom. H); 7.39–7.41 (*m*, 1 arom. H); 7.59–7.69 (*m*, 2 arom. H); 8.47 –8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.8; 20.5; 46.6; 52.0; 54.1; 57.2; 63.8; 122.1; 122.4; 123.1; 127.8; 128.6; 136.6; 136.8; 137.1; 149.0; 149.8; 157.7 (2×); 166.5. APCI-MS (pos.): 339.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 339.2184 ($[M+H]^+$, $C_{20}H_{27}N_4O^+$; calc. 339.2185).

N-*[2-(Dimethylamino)ethyl]*-N-*(pyridin-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide* (**18**). A mixture **18a**/**18b** was synthesized according to *GP 3* by using **16** (30.0 mg, 0.13 mmol, 1.0 equiv.), $Cu(OTf)_2$ (45.1 mg, 0.13 mmol, 1.0 equiv.), and freshly cracked and dist. **12** (42.0 µl, 0.52 mmol, 4.0 equiv.). After of 16 h, the solvent and remaining **12** were removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (25 ml), washed with sat. aq. $NaHCO_3$ soln. (25 ml) and H_2O (25 ml), the org. phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by CC (basic aluminium oxide, CH_2Cl_2/MeOH 98:1 → 95:5) yielded **18a**/**18b** (27.5 mg, 0.09 mmol, 71%; *endo*/*exo* 1.7:1). Slightly brown gum.

Data of **18a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.13–1.17 (*m*, 1 H, CH_2(7)); 1.18–1.44 (*m*, 1 H of CH_2(7), 1 H of CH_2(3)); 1.75–1.82 (*m*, 1 H, CH_2(3)); 2.17 (*s*, Me); 2.18 (*s*, Me); 2.36–2.46 (*m*, CH_2NMe_2); 2.95–3.01 (*m*, CH); 3.07–3.10 (*m*, CH); 3.40–3.52 (*m*, NCH_2CH_2); 3.53–3.61 (*m*, CH(2)); 4.63–4.83 (*m*, CH_2N); 5.94 (*dd*, *J* = 5.6, 2.6, CH=CH); 6.14 (*dd*, *J* = 5.6, 3.3, CH=CH); 7.13–7.23 (*m*, 2 arom. H); 7.59–7.70 (*m*, 1 arom. H); 8.49–8.56 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 30.9; 41.7; 42.7; 45.4; 45.8; 49.8; 53.2; 56.6; 58.0; 120.4; 122.4; 132.4; 136.6; 136.9; 149.8; 158.2; 174.8.

Data of **18b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.05–1.11 (*m*, 1 H, CH_2(7)); 1.31–1.45 (*m*, 1 H of CH_2(7), 1 H of CH_2(3)); 1.87–2.00 (*m*, 1 H, CH_2(3)); 2.17 (*s*, Me); 2.18 (*s*, Me); 2.77–2.82 (*m*, CH); 2.84–2.88 (*m*, CH); 2.89–2.92 (*m*, CH_2NMe_2); 3.40–3.61 (*m*, NCH_2CH_2, CH(2)); 4.63–4.83 (*m*, CH_2N); 6.02 (*dd*, *J* = 5.7, 2.7, CH=CH); 6.09 (*dd*, *J* = 5.7, 2.5, CH=CH); 7.13–7.23 (*m*, 2 arom. H); 7.59–7.70 (*m*, 1 arom. H); 8.49–8.56 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 31.2; 41.5; 44.4; 46.2; 46.3; 49.9; 51.4; 56.6; 58.0; 122.0; 122.1; 132.5; 136.7; 136.9; 149.0; 157.7; 174.8. APCI-MS (pos.): 300.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 300.2077 ($[M+H]^+$, $C_{18}H_{26}N_3O^+$; calc. 300.2076).

Conversion of **16** to **18a**/**18b** was monitored *via GP 5*. HPLC was performed with two *Chiralpak AGP* columns (25 cm), NH_4OAC (0.01M)/^{i}PrOH 1:1, a flow rate of 0.75 ml/min, and detection at 260 nm, resulting in the following t_R values: 6.9 (**16**), 9.3 (**18a**), and 10.5 (**18b**) min. For reaction times for full conversion with and without 1.0 equiv. of chosen metal salts and *endo*/*exo* ratios, see *Table 2*.

Table 2

16 → **18**	*endo*/*exo*	Time [min]
Without	1.5:1	3600
$Cu(OTf)_2$	4.5:1	2200
$CuCl_2$	1.5:1	>2200
CuCl	1.3:1	2000
$FeCl_3$	1.6:1	>3600
$Zn(OTf)_2$	1.5:1	>3600

N-*{2-[Propyl(pyridin-2-ylmethyl)amino]ethyl}*-N-*(pyridin-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide* (**19**). A mixture **19a**/**19b** was synthesized according to *GP 3* by using **17** (0.05 g, 0.15 mmol, 1.0 equiv.), $Cu(OTf)_2$ (54.2 mg, 0.15 mmol, 1.0 equiv.), and freshly cracked and dist. **12** (48 µl, 0.60 mmol, 4.0 equiv.). After 16 h, the solvent and remaining **12** were removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (25 ml), and washed with sat. $NaHCO_3$ soln. (25 ml) and H_2O (25 ml). The org. phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by CC (SiO_2; CH_2Cl_2/MeOH 98:2 → 9:1) furnished **19a**/**19b** (38.8 mg, 96.0 mmol, 64%; *endo*/*exo* 1.5:1). Slightly brown gum.

Data of **19a**: ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.88 (*t*, *J* = 7.3, *Me*CH_2); 1.18–1.27 (*m*, 1 H, CH_2(7)); 1.34–1.45 (*m*, 1 H of CH_2(7), 1 H of CH_2(7)); 1.46–1.55 (*m*, MeCH_2); 1.79–1.87 (*m*, 1 H, CH_2(3)); 2.43–2.52 (*m*, NC$H_2$$CH_2$N); 2.68 (*t*, *J* = 7.2, NC$H_2$$CH_2$N); 2.82–2.90 (*m*, CH); 2.96–3.07 (*m*, CH(2), CH); 3.43–3.65 (*m*, NC$H_2$$CH_2$Me); 4.48 (*s*, C$H_2$N); 4.65–4.83 (*m*, C$H_2$N); 5.98 (*dd*, *J* = 5.6, 2.8, C*H*=CH); 6.20 (*dd*, *J* = 5.6, 3.0, CH=C*H*); 7.10–7.23 (*m*, 3 arom. H); 7.38–7.46 (*m*, 1 arom. H); 7.56–7.70 (*m*, 2 arom. H); 8.47–8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.8; 20.5; 31.0; 41.7; 42.8; 46.2; 49.8; 51.4; 52.9; 53.5; 57.4; 63.8; 121.9; 122.1; 132.5; 132.6; 136.5; 136.7; 136.9; 137.0; 149.1; 149.9; 158.3; 174.5.

Data of **19b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.83 (*t*, *J* = 7.1, *Me*CH_2); 1.19–1.32 (*m*, 1 H, CH_2(7)); 1.31–1.52 (*m*, 1 H, CH_2(7)); 1.46–1.55 (*m*, MeCH_2); 1.70–1.77 (*m*, 1 H, CH_2(3)); 2.20–2.35 (*m*, 1 H, CH_2(3)); 2.41–2.52 (*m*, NC$H_2$$CH_2$N); 2.60–2.73 (*m*, NC$H_2$$CH_2$N); 2.83–2.91 (*m*, CH); 2.96–3.07 (*m*, CH(2), CH); 3.43–3.65 (*m*, NC$H_2$$CH_2$Me); 4.48 (*s*, C$H_2$N); 4.65–4.83 (*m*, C$H_2$N); 6.06 (*dd*, *J* = 5.6, 2.9, C*H*=CH); 6.08 (*dd*, *J* = 5.6, 3.0, CH=C*H*); 7.10–7.23 (*m*, 3 arom. H); 7.38–7.46 (*m*, 1 arom. H); 7.56–7.70 (*m*, 2 arom. H); 8.47–8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.8; 20.5; 31.2; 41.3; 41.4; 46.0; 49.8; 52.0; 52.9; 53.5; 57.4; 60.9; 121.9; 122.1; 132.5; 132.6; 136.5; 136.7; 136.9; 137.0; 149.1; 149.9; 158.3; 174.5. APCI-MS (pos.): 405.3 (100, $[M + H]^+$). HR-APCI-MS (pos.): 405.2654 ($[M + H]^+$, $C_{25}H_{33}N_4O^+$; calc. 405.2654).

Conversion of **17** to **19a**/**19b** was monitored *via GP 5*. HPLC was performed with a chiral ADH column (25 cm), heptane/^{i}PrOH/EtOH 45 : 4 : 1, a flow rate of 1.0 ml/min, and detection at 230 nm resulting in the following t_R values: 15.9 (**19b**), 17.2 + 20.1 (**19a**), and 22.0 (**17**) min. Cycloadduct **19a** was separated by using the chiral *ADH* column. For reaction times for full conversion with and without 1.0 equiv. of chosen metal salts, and *endo*/*exo* ratios, see *Table 3*.

Table 3

17 → **19**	*endo*/*exo*	Time [min]
Without	1.7 : 1	> 10000
$Cu(OTf)_2$	6.2 : 1	1800
$CuCl_2$	1.9 : 1	8600
CuCl	1.7 : 1	> 10000
$FeCl_3$	2.0 : 1	8600
$Zn(OTf)_2$	9.5 : 1	450

*(2*E*)-*N,N*-Diethyl-*N',N'*-bis(pyridin-2-ylmethyl)but-2-enediamide* (**20**). *(2*Z*)-4-(Diethylamino)-4-oxobut-2-enoic acid* was prepared by addition of Et_2NH (3.14 ml, 30.6 mmol, 1.0 equiv.) to a stirred soln. of furan-2,5-dione (3.00 g, 30.6 mmol, 1.0 equiv.) in Et_2O (100 ml) at 0°. After 1 h, the resulting solid was filtered and washed with cold Et_2O. Recrystallization in Et_2O provided the product (2.18 g, 12.7 mmol, 42%). Colorless solid.

Diamide **20** was synthesized according to *GP 1*, by using the acid (0.50 g, 2.92 mmol, 1.5 equiv.) mentioned above and *bis(pyridin-2-ylmethyl)amine* (**5**; 0.39 g, 1.95 mmol, 1.0 equiv.) in DMF. The resulting black gum was purified *via* CC (SiO_2; CH_2Cl_2/MeOH 99 : 1 → 9 : 1) to yield a dark-green oil (0.67 g, 1.90 mmol, 97%; (*E*)/(*Z*) mixture).

The mixture (0.53 g, 1.50 mmol, 1.0 equiv.) was dissolved in MeCN (1.50 ml) in a microwave tube. After addition of piperidine (12.0 ml, 0.12 mmol, 8 mol-%), the mixture was heated under microwave at 120° with 150 W for 45 min [18]. The mixture was dissolved in CH_2Cl_2 (50 ml) and washed with sat. NH_4Cl soln. (20 ml), sat. aq. $NaHCO_3$ soln. (20 ml), and H_2O (20 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure to give **20** (0.52 g, 1.47 mmol, 98%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.14 (*t*, *J* = 7.1, *Me*CH_2); 1.20 (*t*, *J* = 7.2, *Me*CH_2); 3.43 (*q*, *J* = 7.1, MeCH_2); 3.44 (*q*, *J* = 7.2, MeCH_2); 4.84 (*s*, CH_2N); 4.85 (*s*, CH_2N); 7.15–7.20 (*m*, 3 arom. H); 7.31–7.34 (*m*, 1 arom. H); 7.46 (br. *s*, CH=CH); 7.61–7.67 (*m*, 2 arom. H); 8.50–8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.1; 15.1; 41.0; 42.5; 50.9; 53.1; 121.1; 122.5; 122.6; 122.7; 131.0; 132.8; 136.8; 136.9; 149.4; 150.0; 156.2; 157.0; 164.4;

166.5. APCI-MS (pos.): 353.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 353.1973 ($[M+H]^+$, $C_{20}H_{25}N_4O_2^+$; calc. 353.1978).

*(2*E*)-*N*-[2-(Dimethylamino)ethyl]-*N*',*N*'-diethyl-*N*-(pyridin-2-ylmethyl)but-2-enediamide* (**21**). A soln. of (2*Z*)-4-(diethylamino)-4-oxobut-2-enoic acid (0.53 g, 3.07 mmol, 1.1 equiv.) in CH_2Cl_2 (10.0 ml) was stirred at r.t. After the addition of DCC (*N,N'*-dicyclohexylcarbodiimide; 0.63 g, 3.07 mmol, 1.1 equiv.), a soln. of **6** (0.50 g, 2.79 mmol, 1.0 equiv.) was added, and the mixture was stirred for 8 h. The mixture was added to CH_2Cl_2 (50 ml), washed with sat. aq. NH_4Cl soln. (20 ml), sat. $NaHCO_3$ soln. (20 ml), and H_2O (20 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting oil was purified by CC (basic aluminium oxide, CH_2Cl_2/MeOH 99.5 : 0.5 → 94 : 6) to yield a brown gum (0.73 g, 2.20 mmol, 82%; (*E*)/(*Z*) mixture).

The mixture (0.73, 2.20 mmol, 1.0 equiv.) was dissolved in MeCN (10 ml) in a microwave tube. After addition of piperidine (17.4 ml, 0.18 mmol, 8 mol-%), the mixture was heated under microwave at 120° with 150 W for 60 min [18]. The mixture was dissolved in CH_2Cl_2 (50 ml), and washed with sat. NH_4Cl soln. (20 ml), sat. aq. $NaHCO_3$ soln. (20 ml) and H_2O (20 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure to afford **21** (0.69 g, 2.09 mmol, 95%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.12 – 1.25 (*m*, 2 *Me*CH_2); 2.25 (*s*, NMe_2); 2.48 – 2.59 (*m*, NCH_2CH_2N); 3.39 – 3.50 (*m*, 2 $MeCH_2$); 3.58 – 3.66 (*m*, NCH_2CH_2N); 4.82 (*s*, CH_2N); 7.15 – 7.37 (*m*, 2 arom. H); 7.38 (*d*, *J* = 14.8, CH=C*H*); 7.45 (*d*, *J* = 14.7, C*H*=CH); 7.61 – 7.71 (*m*, 1 arom. H); 8.51 – 8.60 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.0; 13.1; 41.0; 41.1; 44.8; 45.4; 45.8; 52.2; 56.7; 121.0; 122.6; 132.3; 132.4; 137.0; 149.9; 156.6; 164.3; 165.6. APCI-MS (pos.): 333.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 333.2289 ($[M+H]^+$, $C_{18}H_{29}N_4O_2^+$; calc. 333.2291).

*(2*E*)-*N*,N-Diethyl-*N*'-{2-[propyl(pyridin-2-ylmethyl)amino]ethyl}-*N*'-(pyridin-2-ylmethyl)but-2-enediamide* (**22**). Diamide **22** was synthesized according to *GP 1*, by using (2*Z*)-4-(diethylamino)-4-oxobut-2-enoic acid (0.54 g, 3.17 mmol, 1.5 equiv.) and **7** (0.60 g, 2.11 mmol, 1.0 equiv.) in DMF. The resulting black gum was purified by CC (SiO_2; CH_2Cl_2/MeOH 99 : 1 → 9 : 1) to yield a dark-green oil (0.92, 2.10 mmol, 99%, (*E*)/(*Z*) mixture).

The mixture (0.69 g, 1.57 mmol, 1.0 equiv.) was dissolved in MeCN (2.0 ml) in a microwave tube. After addition of piperidine (16.7 µl, 8 mol-%), the mixture was heated under microwave at 120° with 150 W for 60 min [18]. The mixture was dissolved in CH_2Cl_2 (80 ml) and washed with sat. NH_4Cl soln. (80 ml), sat. $NaHCO_3$ soln. (80 ml) and H_2O (80 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure to afford **22** (0.67 g, 1.52 mmol, 97%). ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.93 (*t*, *J* = 7.4, *Me*CH_2); 1.16 (*t*, *J* = 7.0, *Me*NCH_2); 1.21 (*t*, *J* = 7.4, *Me*NCH_2); 1.46 – 1.53 (*m*, CH_2CH_2Me); 2.46 – 2.51 (*t*, *J* = 7.5, NCH_2CH_2Me); 2.70 (*t*, *J* = 6.7, NCH_2CH_2N); 3.43 (*q*, *J* = 6.7, $MeCH_2N$); 3.47 (*q*, *J* = 7.2, $MeCH_2N$); 3.60 (*t*, *J* = 6.8, NCH_2CH_2N); 3.75 (*s*, CH_2N); 4.72 (*s*, CH_2N); 7.10 – 7.24 (*m*, CH=CH, 3 arom. H); 7.33 – 7.36 (*m*, 1 arom. H); 7.47 – 7.52 (*d*, *J* = 14.5, C*H*=CH); 7.59 – 7.76 (*m*, 2 arom. H); 8.49 – 8.56 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.8; 13.1 (2 ×); 20.5; 41.1; 42.5; 46.8; 52.1; 53.4; 57.0; 60.8; 122.0; 122.2; 122.7; 123.1; 130.8; 132.1; 136.4; 136.8; 149.0; 149.4; 157.4 (2 ×); 164.4; 165.6. ESI-MS (pos.): 438.3 (100, $[M + H]^+$). HR-ESI-MS (pos.): 438.2864 ($[M+H]^+$, $C_{25}H_{36}N_5O_2^+$; calc. 438.2869).

*Ethyl (2*E*)-4-[Bis(pyridin-2-ylmethyl)amino]-4-oxobut-2-enoate* (**23**). Ester **23** was synthesized according to *GP 1*, by using ethyl fumarate (3.05 g, 21.0 mmol, 1.5 equiv.), and **5** (2.80 g, 14.0 mmol, 1.0 equiv.) in CH_2Cl_2. The resulting brown oil was purified by CC (SiO_2; CH_2Cl_2/MeOH 99 : 1 → 9 : 1) to yield **23** (3.73 g. 11.5 mmol, 82%). Slightly brown oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.27 – 1.31 (*t*, *J* = 7.2, *Me*OCH_2O); 4.18 – 4.24 (*q*, *J* = 7.2, $MeOCH_2O$); 4.84 (*s*, CH_2N); 4.86 (*s*, CH_2N); 6.88 – 6.92 (*d*, *J* = 15.3, CH(2)); 7.18 – 7.23 (*m*, 3 arom. H); 7.38 – 7.42 (*m*, 1 arom. H); 7.47 – 7.52 (*d*, *J* = 15.3, CH(3)); 7.63 – 7.72 (*m*, 2 arom. H); 8.48 – 8.57 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.1; 51.4; 53.2; 61.1; 121.3; 122.7 (2 ×); 128.3; 132.1; 133.9; 136.9; 137.4; 148.6; 150.0; 155.9; 156.4; 165.6; 165.9. ESI-MS (pos.): 326.0 (100, $[M + H]^+$). Anal. calc. for $C_{18}H_{19}N_3O_3$ (325.36): C 66.45, H 5.89, N 12.91; found: C 66.27, H 6.00, N 12.73.

*Ethyl (2*E*)-4-{[2-(Dimethylamino)ethyl](pyridin-2-ylmethyl)amino}-4-oxobut-2-enoate* (**24**). Oxalyl chloride (3.44 ml, 39.5 mmol, 2.5 equiv.) was added to a stirred suspension of ethyl fumarate (2.28 g, 15.8 mmol, 1.0 equiv.) in CH_2Cl_2 (20.0 ml) at r.t. After addition of DMAP ((4-dimethylamino)pyridine; 1 drop), the resulting soln. was stirred for 1.5 h, and the solvent was removed under reduced pressure. The

crude product was purified by bulb-to-bulb distillation and yielded a colorless oil (2.40 g, 14.7 mmol, 93%; [19]: 96%).

A soln. of **6** (0.40 g, 2.01 mmol, 1.0 equiv.) in CH_2Cl_2 (10.0 ml) was cooled to 0° and freshly distilled fumaric acid ethyl ester chloride (0.89 g, 5.48 mmol, 2.5 equiv.) was added in one portion. After stirring at 0°, for 1 h, the soln. was warmed up to r.t., and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 ml), and the org. soln. was washed with a sat. aq. soln. of $NaHCO_3$ (20 ml) and H_2O (2 × 20 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting oil was purified by CC (basic aluminium oxide, CH_2Cl_2/MeOH 99.5 : 0.5 → 9 : 1) to yield **24** (0.55 g. 1.70 mmol, 85%). Brown gum. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.25 – 1.35 (*m*, *Me*CH_2); 2.23 (*s*, MeN); 2.25 (*s*, MeN); 2.44 – 2.54 (*m*, NCH_2CH_2N); 3.53 – 3.63 (*m*, NCH_2CH_2N); 4.17 – 4.29 (*m*, MeCH_2); 4.79 (*s*, CH*H*N); 4.80 (*s*, CH*H*N); 6.85 (*d*, *J* = 15.3, C*H*=CH); 7.16 – 7.32 (*m*, 2 arom. H); 7.45 (*d*, *J* = 15.4, CH=C*H*); 7.60 – 7.71 (*m*, 1 arom. H); 8.50 – 8.60 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.2; 45.6; 45.8; 53.9; 56.9; 58.4; 61.1; 121.0; 122.5; 122.8; 131.7; 134.0; 136.9; 150.0; 157.5; 165.9. APCI-MS (pos.): 306.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 306.1814 ($[M+H]^+$, $C_{16}H_{24}N_3O_3^+$; calc. 306.1818).

*Ethyl (2*E*)-4-Oxo-4-[{2-[propyl(pyridin-2-ylmethyl)amino]ethyl}(pyridin-2-ylmethyl)amino]but-2-enoate* (**25**). Ester **25** was synthesized according to *GP 1* by using ethyl fumarate (0.38 g, 2.60 mmol, 1.5 equiv.) and **7** (0.49 g, 1.70 mmol, 1.0 equiv.) in CH_2Cl_2. The residue was dissolved in CH_2Cl_2 (20 ml), and the org. soln. was washed with a sat. aq. $NaHCO_3$ soln. (20 ml) and H_2O (20 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting brown oil was purified by CC (SiO_2; CH_2Cl_2/MeOH 99 : 1 → 9 : 1) to yield **25** (0.49 g, 1.30 mmol, 72%). Slightly brown oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.80 – 0.83 (*t*, *J* = 7.5, *Me*CH_2); 1.27 – 1.31 (*t*, *J* = 7.2, *Me*OCH_2O); 1.50 – 1.53 (*m*, MeCH_2CH_2); 2.48 – 2.51 (m_c, NCH_2CH_2Me); 2.68 (*m*, NCH_2CH_2N); 3.55 (*m*, NCH_2CH_2N); 4.18 – 4.24 (*q*, *J* = 7.2, MeCH_2O); 4.65 (*s*, CH_2N); 4.75 (*s*, CH_2N); 6.88 – 6.92 (*d*, *J* = 15.3, CH=CH_{ester}); 7.10 – 7.22 (*m*, 3 arom. H); 7.25 – 7.28 (*m*, 1 arom. H); 7.47 – 7.52 (*d*, *J* = 15.3, CH=CH_{amide}); 7.56 – 7.62 (*m*, 2 arom. H); 8.45 – 8.51 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.8; 14.2; 20.2; 46.8; 51.9; 53.0; 54.0; 57.0; 61.1; 122.8; 123.0; 123.2; 123.3; 128.5; 131.9; 136.9; 137.0; 149.2; 150.1; 156.7 (2×); 159.1; 166.0. CI-MS (NH_3): 411.2 (100, $[M + H]^+$). HR-CI-MS (NH_3): 411.2392 ($[M+H]^+$, $C_{23}H_{31}N_4O_3^+$; calc. 411.2396).

N,N-*Diethyl*-N',N'-*bis(pyridin-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide* (**26**). A mixture **26a**/**26b** was synthesized according to *GP 2*, by using **20** (0.15 g, 0.44 mmol, 1.0 equiv.), $Cu(OTf)_2$ (0.16 g, 0.44 mmol, 1.0 equiv.), and freshly cracked and dist. **12** (0.15 ml, 1.76 mmol, 4.0 equiv.). After 16 h, removal of solvent and remaining **12** under reduced pressure, the crude product was dissolved in CH_2Cl_2 (25 ml), washed with a sat. aq. soln. of $NaHCO_3$ (20 ml) and H_2O (20 ml), and dried (Na_2SO_4). After evaporation of the solvent, purification by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) yielded **246a**/**26b** (0.11 g, 0.26 mmol, 60%; *endo*/*exo* 2.8 : 1). Slightly brown gum.

Data of **26a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.16 (*t*, *J* = 7.1, *Me*CH_2); 1.20 (*t*, *J* = 6.8, *Me*CH_2); 1.37 (*ddd*, *J* = 8.5, 3.2, 1.6, 1 H, CH_2); 1.98 (*ddd*, *J* = 8.5, 1.6, 1.6, 1 H, CH_2); 2.85 – 2.87 (*m*, H_{syn}); 3.06 – 3.20 (*m*, 2 CH); 3.28 – 3.48 (*m*, 2 MeCH_2); 3.79 (*dd*, *J* = 4.6, 3.4, H_{anti}); 4.51 – 5.02 (*m*, 2 CH_2N); 6.10 – 6.05 (*dd*, *J* = 5.6, 2.9, C*H*=CH); 6.36 (*dd*, *J* = 5.6, 3.0, CH=C*H*); 7.11 – 7.26 (*m*, 4 arom. H); 7.58 – 7.68 (*m*, 2 arom. H); 8.50 – 8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 31.0 (2×); 41.7; 42.9; 46.3; 49.8; 51.4; 53.0 (2×); 120.7 (2×); 122.2; 122.3; 132.5 (2×); 136.9; 137.0; 149.9; 150.0; 157.4; 157.8; 175.2 (2×).

Data of **26b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.99 (*t*, *J* = 7.1, *Me*CH_2); 1.06 (*t*, *J* = 7.1, *Me*CH_2); 1.43 (*ddd*, *J* = 8.3, 3.3, 1.7, 1 H, CH_2); 2.01 (*ddd*, *J* = 8.4, 1.9, 1.6, 1 H, CH_2); 2.92 – 3.02 (*m*, H_{syn}); 3.06 – 3.20 (*m*, 2 CH); 3.28 – 3.48 (*m*, 2 MeCH_2); 3.64 (*dd*, *J* = 4.9, 3.5, H_{anti}); 4.51 – 5.02 (*m*, 2 CH_2N); 6.00 (*dd*, *J* = 5.6, 3.0, CH=C*H*); 6.22 (*dd*, *J* = 5.6, 3.2, C*H*=CH); 7.11 – 7.26 (*m*, 4 arom. H); 7.58 – 7.68 (*m*, 2 arom. H); 8.50 – 8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 31.5 (2×); 40.9; 41.8; 46.6; 46.9; 51.5; 52.8 (2×); 120.7 (2×); 122.2; 122.4; 136.1; 136.7; 136.8; 138.3; 149.2 (2×); 157.2; 157.8; 176.8 (2×). CI-MS (NH_3): 419.3 (100, $[M + H]^+$). HR-CI-MS (NH_3): 419.2444 ($[M+H]^+$, $C_{25}H_{31}N_4O_2^+$; calc. 419.2447).

Conversion of **20** to **26a**/**26b** was monitored *via GP 5*. HPLC was performed with a chiral *ODH* column (25 cm) using heptane/^{i}PrOH (5 : 1) as solvent. HPLC-runs were performed with a flow rate of 0.5 ml/min, and detection at 210 nm resulting in the following t_R values: 20.0 + 21.8 (**26b**), 26.6 (**26a**), and 35.7 (**20**) min. Separation of **26b** was possible, using the chiral *ODH* column. For reaction times for full conversion with and without 1.0 equiv. of chosen metal salts, and *endo*/*exo* ratios, see *Table 4*.

Table 4

20 → **26**	*endo*/*exo*	Time [min]
Without	2.8 : 1	800
$Cu(OTf)_2$	3.5 : 1	450
$CuCl_2$	3.2 : 1	700
CuCl	3.0 : 1	900
$FeCl_3$	3.2 : 1	900
$Zn(OTf)_2$	3.5 : 1	700

N-*[2-(Dimethylamino)ethyl]*-N',N'-*diethyl*-N-*(pyridin-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide* (**27**). A mixture of **27a**/**27b** was synthesized according to *GP 2* by using **21** (50.0 mg, 0.15 mmol, 1.0 equiv.), $Cu(OTf)_2$ (54.2 mg, 0.15 mmol, 1.0 equiv.), and freshly cracked and dist. **12** (49.7 µl, 0.60 mmol, 4.0 equiv.). After 16 h, removal of solvent and remaining **12** under reduced pressure, the crude product was dissolved in CH_2Cl_2 (25 ml), and washed with a sat. aq. soln. of $NaHCO_3$ (20 ml) and H_2O (20 ml). After drying the org. phase (Na_2SO_4), the solvent was removed under reduced pressure. Purification by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) yielded **27a**/**27b** (41.0 mg, 0.10 mmol, 69%; *endo*/*exo* ratio of 2.5 : 1). Slightly brown gum.

Data of **27a**: ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.04 – 1.22 (*m*, 2 *Me*CH_2); 1.32 – 1.38 (*m*, 1 H, CH_2(7)); 1.99 – 2.03 (*m*, 1 H, CH_2(7)); 2.30 (*s*, Me); 2.41 (*s*, Me); 2.51 – 2.65 (*m*, C*H*$_2$NMe_2); 2.83 – 2.89 (*m*, CH); 2.96 – 3.01 (*m*, CH); 3.25 – 3.49 (*m*, NC*H*$_2$CH_2N, 2 NC*H*$_2$Me); 3.51 – 3.59 (*m*, CH); 3.63 – 3.68 (*m*, CH); 4.42 – 4.94 (*m*, CH_2N); 6.09 (*dd*, *J* = 5.3, 2.9, C*H*=CH); 6.17 (*dd*, *J* = 5.4, 3.2, CH=C*H*); 7.13 – 7.23 (*m*, 2 arom. H); 7.59 – 7.70 (*m*, 1 arom. H); 8.49 – 8.56 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.5; 14.8; 40.2; 41.7; 44.8; 45.2; 45.9; 46.7; 48.6; 49.0; 51.8; 53.7; 56.1; 57.8; 122.0; 122.7; 134.2; 134.5; 136.6; 136.7; 149.2; 171.6; 171.8.

Data of **27b**: ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.04 – 1.22 (*m*, 2 *Me*CH_2); 1.40 – 1.46 (*m*, C*H*H); 1.91 – 1.98 (*m*, C*H*H); 2.30 (*s*, Me); 2.37 (*s*, Me); 2.51 – 2.65 (*m*, C*H*$_2$NMe_2); 3.06 – 3.29 (*m*, 2 CH); 3.25 – 3.49 (*m*, NC*H*$_2$CH_2, 2 NC*H*$_2$Me); 3.51 – 3.59 (*m*, CH); 3.70 – 3.76 (*m*, CH); 4.42 – 4.94 (*m*, pyC*H*$_2$N); 6.00 – 6.05 (*m*, C*H*=CH); 6.33 – 6.37 (*m*, C*H*=CH); 7.13 – 7.23 (*m*, 2 arom. H); 7.59 – 7.70 (*m*, 1 arom. H); 8.49 – 8.56 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 13.0; 13.1; 40.5; 42.0; 44.7; 45.2; 45.8; 46.6; 48.9 (2×); 51.7; 53.5; 56.0; 58.0; 122.2; 122.6; 134.4; 134.7; 136.9; 137.0; 149.8; 173.2; 173.5. APCI-MS (pos.): 399.3 (100, $[M + H]^+$). HR-APCI-MS (pos.): 399.2758 ($[M + H]^+$, $C_{23}H_{35}N_4O_2^+$; calc. 399.2760).

Conversion of **21** to **27a**/**27b** was monitored *via GP 5*. HPLC was performed with a *Luna C8* column (25 cm), MeCN/aq. NH_4OAc (0.01M) 1 : 1, a flow rate of 1.0 ml/min and detection at 270 nm, resulting in the following t_R values: 4.20 (**21**) and 5.45 (**27a** + **27b**) min. For reaction times for full conversion with and without 1.0 equiv. of chosen metal-salts and *endo*/*exo* ratios, see *Table 5*.

Table 5

21 → **27**	*endo*/*exo*	Time [min]
Without	2.5 : 1	1400
$Cu(OTf)_2$	2.5 : 1	1100
$CuCl_2$	2.5 : 1	1250
CuCl	2.5 : 1	900
$FeCl_3$	2.5 : 1	1400
$Zn(OTf)_2$	2.5 : 1	1500

N,N-*Diethyl*-N'-*{2-[propyl(pyridin-2-ylmethyl)amino]ethyl}*-N'-*(pyridin-2-ylmethyl)bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxamide* (**28**). A mixture **28a**/**28b** was synthesized according to *GP 2* by using **22** (45.0 mg, 0.10 mmol, 1.0 equiv.), $Zn(OTf)_2$ (37.4 mg, 0.10 mmol, 1.0 equiv.), and freshly cracked and dist.

12 (34.0 µl, 0.41 mmol, 4.0 equiv.). After 16 h, removal of solvent and remaining **12** under reduced pressure, the crude product was dissolved in CH_2Cl_2 (25 ml), washed with a sat. aq. soln. of $NaHCO_3$ (20 ml) and H_2O (20 ml), dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) yielded **28a**/**28b** (29.8 mg, 0.06 mmol, 58%; *endo*/*exo* of 1.7 : 1). Slightly brown gum.

Data of **28a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.80 – 0.82 (*t*, *J* = 8.3, *Me*CH_2); 1.03 – 1.21 (*m*, 2 *Me*CH_2); 1.32 – 1.41 (*m*, C*H*H); 1.42 – 1.55 (*m*, MeC*H*$_2$); 1.91 – 2.03 (*m*, 1 H, CH_2(7); 2.41 – 2.54 (*m*, NC*H*$_2$C*H*$_2$N); 2.70 – 2.76 (*m*, CH); 2.82 – 2.89 (*m*, CH); 2.95 – 3.04 (*m*, CH); 3.11 – 3.22 (*m*, NC*H*$_2$CH$_2$N); 3.25 – 3.51 (*m*, NC*H*$_2$CH$_2$Me, 2 NC*H*$_2$Me); 3.65 – 3.68 (*m*, CH); 3.73 (*s*, C*H*$_2$N); 4.41 – 4.87 (*m*, C*H*$_2$N); 5.94 – 6.06 (*m*, C*H*=CH); 6.16 – 6.27 (*m*, CH=C*H*); 7.10 – 7.30 (*m*, 3 arom. H); 7.39 – 7.41 (*m*, 1 arom. H); 7.59 – 7.69 (*m*, 2 arom. H); 8.47 – 8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.9; 14.7 (2 ×); 20.7; 40.1; 40.5; 41.6; 42.0; 44.9; 45.0; 46.7; 47.7; 48.9; 51.8; 53.6; 57.2; 122.1 (2 ×); 134.4; 134.6; 136.5; 136.6; 137.1; 137.2; 158.2 (2 ×); 173.4; 174.9.

Data of **28b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.80 – 0.82 (*t*, *J* = 8.3, *Me*CH_2); 1.03 – 1.21 (*m*, 2 *Me*CH_2); 1.32 – 1.41 (*m*, 1 H, CH_2(7)); 1.42 – 1.55 (*m*, MeC*H*$_2$); 1.91 – 2.03 (*m*, 1 H, CH_2(7)); 2.41 – 2.54 (*m*, NC*H*$_2$CH$_2$N); 2.70 – 2.76 (*m*, CH); 2.82 – 2.89 (*m*, CH); 2.95 – 3.04 (*m*, CH); 3.11 – 3.22 (*m*, NC*H*$_2$CH$_2$N); 3.25 – 3.51 (*m*, NC*H*$_2$CH$_2$Me, 2 NC*H*$_2$); 3.65 – 3.68 (*m*, CH); 3.73 (*s*, C*H*$_2$N); 4.41 – 4.87 (*m*, C*H*$_2$N); 5.94 – 6.06 (*m*, C*H*=CH); 6.30 – 6.36 (*m*, CH=C*H*); 7.10 – 7.30 (*m*, 3 arom. H); 7.39 – 7.41 (*m*, 1 arom. H); 7.59 – 7.69 (*m*, 2 arom. H); 8.47 – 8.58 (*m*, 2 arom. H). APCI-MS (pos.): 504.3 (100, $[M + H]^+$). HR-APCI-MS (pos.): 504.3336 ($[M + H]^+$, $C_{30}H_{42}N_5O_2^+$; calc. 504.3339).

Conversion of **22** to **28a**/**28b** was monitored *via GP 5*. HPLC was performed with a *Luna C8* column (25 cm), aq. NH_4OAc (0.01M)/MeCN 4 : 6 → 6 : 4, a flow rate of 0.5 ml/min, and detection at 270 nm, resulting in the following t_R values: 8.7 (**22**), 12.3 (**28a**), and 12.8 (**28b**) min. For reaction times for full conversion with and without 1.0 equiv. of chosen metal salts and *endo*/*exo* ratios, see *Table 6*.

Table 6

22 → **28**	*endo*/*exo*	Time [min]
Without	1.7 : 1	4800
$Cu(OTf)_2$	1.7 : 1	3000
$CuCl_2$	1.7 : 1	> 4800
CuCl	1.7 : 1	> 4800
$FeCl_3$	1.7 : 1	> 4800
$Zn(OTf)_2$	1.7 : 1	2000

Ethyl 3-[Bis(pyridin-2-ylmethyl)carbamoyl]bicyclo[2.2.1]hept-5-ene-2-carboxylate (**29**). A mixture **29a**/**29b** was synthesized according to *GP 2* by using **23** (0.12 g, 0.37 mmol, 1.0 equiv.) and freshly cracked and dist. **12** (0.13 µl, 1.48 mmol, 4.0 equiv.). After 16 h, removal of solvent and remaining **12** under reduced pressure, the crude product was dissolved in CH_2Cl_2 (25 ml), and washed with a sat. aq. soln. of $NaHCO_3$ (25 ml) and H_2O (25 ml), and dried (Na_2SO_4). Purification by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) yielded **29a**/**29b** (0.12 g, 0.16 mmol, 83%; *endo*/*exo* of 0.4 : 1). Slightly brown gum.

Data of **29a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.20 (*t*, *J* = 7.1, *Me*CH_2); 1.41 – 1.46 (*m*, 1 H, CH_2(7)); 1.97 – 2.02 (*m*, 1 H, CH_2(7)); 2.78 – 2.83 (*m*, CH); 2.91 – 2.93 (*m*, CH); 3.25 – 3.29 (*m*, CH); 3.58 – 3.61 (*m*, CH); 3.93 – 4.03 (*m*, MeC*H*$_2$); 4.60 – 5.02 (*m*, 2 CH_2N); 6.03 – 6.05 (*dd*, *J* = 5.6, 2.9, CH=C*H*); 6.17 – 6.22 (*dd*, *J* = 5.6, 3.0, C*H*=CH); 7.16 – 7.35 (*m*, 4 arom. H); 7.63 – 7.72 (*m*, 2 arom. H); 8.47 – 8.57 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 45.4 (2 ×); 46.7; 48.0; 48.1; 48.2; 51.3; 53.1; 60.7; 121.0; 121.2; 134.1; 135.8; 137.0; 137.2; 149.8 (2 ×); 157.2; 157.3; 174.8; 175.0.

Data of **29b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.16 (*t*, *J* = 7.1, *Me*CH_2); 1.41 – 1.46 (*m*, 1 H, CH_2(7)); 1.55 – 1.59 (*m*, 1 H, CH_2(7)); 2.91 – 2.93 (*m*, CH); 3.13 – 3.16 (*m*, 2 CH); 3.63 – 3.66 (*m*, CH); 4.01 – 4.11 (*m*, MeC*H*$_2$); 4.60 – 5.02 (*m*, 2 CH_2N); 6.02 – 6.04 (*dd*, *J* = 5.3, 3.2, C*H*=CH); 6.33 – 6.37 (*dd*, *J* = 5.2, 3.0, CH=C*H*); 7.16 – 7.35 (*m*, 4 arom. H); 7.63 – 7.72 (*m*, 2 arom. H); 8.47 – 8.57 (*m*, 2 arom. H). ^{13}C-NMR

($CDCl_3$, 100 MHz): 44.7 (2 x); 45.7; 46.9; 48.4; 48.8; 51.5; 53.2; 60.4; 122.5 (2 ×); 155.7 (2 ×); 137.7 (2 ×); 149.6 (2 ×); 156.7 (2 ×); 173.7 (2 ×). APCI-MS (pos.): 392.2 (100, $[M + H]^+$). Anal. calc. for $C_{23}H_{25}N_3O_3$ (391.46): C 70.57, H 6.44, N 10.73; found: C 69.97, H 6.51, N 10.43.

Conversion of **23** to **29a**/**29b** was monitored *via GP 5*. HPLC was performed with a chiral *ADH* column (25 cm), heptane/^{i}PrOH 2 : 1, a flow rate of 0.5 ml/min, and detection at 210 nm resulting in the following t_R values: 18.3 + 24.9 (**29a**), 28.3 (**29b**), and 31.2 (**23**) min. Separation of **29b** was using the chiral *ADH* column. For reaction times for full conversion with and without 1.0 equiv. of chosen metal-salts, and *endo*/*exo* ratios, see *Table 7*.

Table 7

23 → **29**	*endo*/*exo*	Time [min]
Without	0.4 : 1	160
$Cu(OTf)_2$	1.0 : 1	25
$CuCl_2$	0.5 : 1	160
CuCl	0.5 : 1	160
$FeCl_3$	0.5 : 1	250
$Zn(OTf)_2$	0.4 : 1	160

Ethyl 3-{[2-(Dimethylamino)ethyl](pyridin-2-ylmethyl)carbamoyl}bicyclo[2.2.1]hept-5-ene-2-carboxylate (**30**). A mixture **30a**/**30b** was synthesized according to *GP 2* by using **24** (37.0 mg, 0.11 mmol, 1.0 equiv.) and freshly cracked and dist. **12** (38.0 µl, 0.44 mmol, 4.0 equiv.). After 16 h, removal of solvent and remaining **12** under reduced pressure, the crude product was dissolved in CH_2Cl_2 (20 ml), and washed with a sat. aq. soln. of $NaHCO_3$ (20 ml) and H_2O (20 ml). After drying (Na_2SO_4) and evaporation of the solvent, the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) to yield **30a**/**30b** (29.7 mg, 0.08 mmol, 69%; *endo*/*exo* of 0.2 : 1). Slightly brown gum.

Data of **30a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.16 (*t*, *J* = 7.1, *Me*CH_2); 1.39 – 1.46 (*m*, 1 H, CH_2(7)); 1.95 – 2.04 (*m*, 1 H, CH_2(7)); 2.24 (*s*, Me); 2.25 (*s*, Me); 2.42 – 2.54 (*m*, CH_2NMe_2); 2.78 – 2.84 (*m*, CH); 2.87 – 2.96 (*m*, CH); 3.52 – 3.64 (*m*, NC$H_2$$CH_2$); 3.03 – 3.14 (*m*, CH); 3.68 – 3.77 (*m*, CH); 3.93 – 4.16 (*m*, MeCH_2); 4.58 – 5.02 (*m*, CH_2N); 6.05 (*dd*, *J* = 5.8, 2.7, C*H*=CH); 6.32 (*dd*, *J* = 5.6, 3.0, CH=C*H*); 7.14 – 7.24 (*m*, 2 arom. H); 7.59 – 7.71 (*m*, 1 arom. H); 8.49 – 8.59 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.3; 44.4; 45.0; 45.6; 45.8 (2 ×); 46.4; 46.7; 48.5; 48.8; 56.9; 58.2; 60.4; 120.9; 122.5; 135.7; 136.9; 137.7; 149.8; 158.1; 174.4 (2 ×).

Data of **30b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.24 (*t*, *J* = 7.1, *Me*CH_2); 1.39 – 1.46 (*m*, 1 H, CH_2(7)); 1.95 – 2.04 (*m*, 1 H, CH_2(7)); 2.24 (*s*, Me); 2.25 (*s*, Me); 2.42 – 2.54 (*m*, CH_2NMe_2); 2.78 – 2.84 (*m*, CH); 2.87 – 2.96 (*m*, CH); 3.52 – 3.64 (*m*, NC$H_2$$CH_2$); 3.22 – 3.32 (*m*, CH); 3.33 – 3.47 (*m*, CH); 3.93 – 4.16 (*m*, MeCH_2); 4.58 – 5.02 (*m*, CH_2N); 6.14 (*dd*, *J* = 5.6, 2.8, C*H*=CH); 6.17 (*dd*, *J* = 5.6, 3.0, CH=C*H*); 7.14 – 7.24 (*m*, 2 arom. H); 7.59 – 7.71 (*m*, 1 arom. H); 8.49 – 8.59 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 14.4; 44.4; 44.8; 45.6; 45.8 (2 ×); 46.8; 46.9; 48.5; 48.8; 56.9; 58.2; 60.4; 121.8; 122.2; 136.0; 136.8; 137.7; 149.2; 158.1; 174.4; 174.5. APCI-MS (pos.): 372.2 (100, $[M + H]^+$). HR-APCI-MS (pos.): 372.22840 ($[M+H]^+$, $C_{21}H_{30}N_3O_3^+$; calc. 372.22872).

Conversion of **24** to **30a**/**30b** was monitored *via GP 5*. HPLC was performed with a chiral *ODH* column (25 cm), heptane/^{i}PrOH/EtOH 361 : 38 : 1, a flow rate of 0.5 ml/min, and detection at 210 nm, resulting in the following t_R values: 16.4 + 18.3 (**30b**), 21.5 (**30a**), and 29.7 (**24**) min. Separation of **30b** was possible using of the chiral *ODH* column. For reaction times for full conversion with and without 1.0 equiv. of chosen metal salts, and *endo*/*exo* ratios, see *Table 8*.

Ethyl 3-[[2-[Propyl(pyridin-2-ylmethyl)amino]ethyl](pyridin-2-ylmethyl)carbamoyl]bicyclo[2.2.1]-hept-5-ene-2-carboxylate (**31**). A mixture **31a**/**31b** was synthesized according to *GP 2* by using **25** (0.10 mg, 0.26 mmol, 1.0 equiv.) and freshly cracked and dist. **12** (85.0 µl, 1.0 mmol, 4.0 equiv.). After 16 h, removal of solvent and remaining **12** under reduced pressure, the crude product was dissolved in CH_2Cl_2 (25 ml), and washed with a sat. aq. soln. of $NaHCO_3$ (20 ml) and H_2O (20 ml). The org. phase was

Table 8

24 → **30**	*endo*/*exo*	Time [min]
Without	0.2 : 1	80
$Cu(OTf)_2$	0.2 : 1	30
$CuCl_2$	0.2 : 1	80
CuCl	0.2 : 1	10
$FeCl_3$	0.2 : 1	80
$Zn(OTf)_2$	0.2 : 1	80

dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by CC (SiO_2; CH_2Cl_2/MeOH 98 : 2 → 9 : 1) yielded **31a**/**31b** (75.0 mg, 0.16 mmol, 60%; *endo*/*exo* of 0.4 : 1). Slightly brown gum.

Data of **31a**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.89 (*t*, *J* = 7.3, *Me*CH_2CH_2); 1.15 (*t*, *J* = 7.1, *Me*OCH_2); 1.36 – 1.43 (*m*, C*H*H); 1.45 – 1.60 (*m*, MeCH_2CH_2); 1.91 – 2.01 (*m*, 1 H, CH_2(7)); 2.44 – 2.56 (*m*, NCH_2CH_2Me); 2.67 – 2.79 (*m*, NCH_2CH_2N); 2.79 – 2.92 (*m*, 2 CH); 3.10 – 3.18 (*m*, CH); 3.22 – 3.30 (*m*, CH); 3.58 – 3.64 (*m*, NCH_2CH_2N); 3.73 (*s*, CH_2N); 3.93 – 4.13(*m*, MeOCH_2O); 4.47 – 4.95 (*m*, CH_2N); 5.88 – 6.05 (*m*, C*H*=CH); 6.12 – 6.34 (*m*, CH=C*H*); 7.10 – 7.23 (*m*, 3 arom. H); 7.40 – 7.47 (*m*, 1 arom. H); 7.58 – 7.70 (*m*, 2 arom. H); 8.47 – 8.58 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 11.8; 14.2; 20.3; 44.4; 45.5; 45.7; 46.7; 46.9; 48.3; 48.6 (2 ×); 52.0; 60.4; 60.6; 122.1 (2 ×); 135.7; 135.9; 136.7; 136.8; 136.9; 137.6; 149.2; 149.7; 157.9; 158.0; 173.7; 173.9.

Data of **31b**. ^{1}H-NMR ($CDCl_3$, 400 MHz): 0.89 (*t*, *J* = 7.3, *Me*CH_2CH_2); 1.21 (*t*, *J* = 7.1, *Me*OCH_2); 1.36 – 1.43 (*m*, 1 H, CH_2(7)); 1.45 – 1.60 (*m*, MeCH_2CH_2); 1.91 – 2.01 (*m*, 1 H, CH_2(7)); 2.44 – 2.56 (*m*, NCH_2CH_2Me); 2.67 – 2.79 (*m*, NCH_2CH_2N); 2.79 – 2.92 (*m*, 2 CH); 2.98 – 3.07 (*m*, CH); 3.22 – 3.30 (*m*, CH); 3.58 – 3.64 (*m*, NCH_2CH_2N); 3.73 (*s*, CH_2N); 3.93 – 4.13(*m*, MeOCH_2O); 4.47 – 4.95 (*m*, CH_2N); 6.02 – 6.05 (*m*, C*H*=CH); 6.12 – 6.17 (*m*, CH=C*H*); 7.10 – 7.23 (*m*, 3 arom. H); 7.40 – 7.47 (*m*, 1 arom. H); 7.58 – 7.70 (*m*, 2 arom. H); 8.47 – 8.58 (*m*, 2 arom. H). CI-MS (NH_3): 477.2 (100, $[M + H]^+$). HR-CI-MS (NH_3): 476.2784 ($[M+H]^+$, $C_{28}H_{36}N_4O_3^+$; calc. 476.2787).

Conversion of **25** to **31a**/**31b** was monitored *via GP 5*. HPLC was performed with a *RP 18XTerra* column (25 cm), MeOH/aq. NH_4OAc (0.01M) 6 : 4, a flow rate of 1.0 ml/min, and detection at 260 nm resulting in the following t_R values: 10.0 (**25**), 15.7 (**31a**), and 17.5 (**31b**) min. For reaction times for full conversion with and without 1.0 equiv. of chosen metal salts, and *endo*/*exo* ratios, see *Table 9*.

Table 9

25 → **31**	*endo*/*exo*	Time [min]
Without	0.4 : 1	400
$Cu(OTf)_2$	0.9 : 1	240
$CuCl_2$	0.9 : 1	400
CuCl	0.8 : 1	400
$FeCl_3$	0.8 : 1	450
$Zn(OTf)_2$	1.0 : 1	70

REFERENCES

[1] X. Peng, J. Du, J. Fan, J. Wang, Y. Wu, J. Zhao, S. Sun, T. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 1500.
[2] J. C. Araya, J. Gajardo, S. A. Moya, P. Aguirre, L. Toupet, J. A. G. Williams, M. Escadeillas, H. Le Bozec, V. Guerchais, *New J. Chem.* **2010**, *34*, 21.
[3] T. Sakamoto, A. Ojida, I. Hamachi, *Chem. Commun.* **2009**, 141.
[4] D. S. Marlin, D. G. Cabrera, D. A. Leigh, A. M. Z. Slawin, *Angew. Chem., Int. Ed.* **2006**, *45*, 1385.

[5] S. Takebayashi, S. Shinkai, M. Ikeda, M. Tekeuchi, *Org. Biomol. Chem.* **2008**, *6*, 493.
[6] R. P. Houghton, R. R. Puttner, *J. Chem. Soc. D, Chem. Commun.* **1970**, 1270.
[7] M. C. Bröhmer, W Bannwarth, *Eur. J. Org. Chem.* **2008**, 4412; M. C. Bröhmer, W. Bannwarth, *Synfacts* **2008**, 1226.
[8] R. A. Kramer, M. C. Bröhmer, N. V. Forkel, W. Bannwarth, *Eur. J. Org. Chem*. **2009**, 4273.
[9] M. C. Bröhmer, S. Mundinger, S. Bräse, W. Bannwarth, *Angew. Chem., Int. Ed.* **2011**, *50*, 6175.
[10] S. Mundinger, U. Jakob, P. Bichovski, W. Bannwarth, *J. Org. Chem*. **2012**, *77*, 8968.
[11] S. Mundinger, U. Jakob, W. Bannwarth, *Chem. – Eur. J.* **2014**, *20*, 1258.
[12] S. Scherbakow, M. Keller, W. Bannwarth, *Eur. J. Org. Chem.* **2014**, 5331.
[13] J. Sauer, R. Sustmann, *Angew. Chem., Int. Ed.* **1980**, *19*, 779.
[14] K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57.
[15] J. Sauer, *Angew. Chem., Int. Ed.* **1966**, *5*, 211.
[16] P. A. Grieco, J. J. Nunes, M. D. Gaul, *J. Am. Chem. Soc.* **1990**, *112*, 4595.
[17] R. Knorr, A. Trzeciak, W. Bannwarth, D. Gillessen, *Tetrahedron Lett.* **1989**, *30*, 1927.
[18] V. Majce, M. Kočevar, S. Polanc, *Tetrahedron Lett.* **2011**, *52*, 3287.
[19] S. E. Denmark, A. Thorarensen, D. S. Middleton, *J. Am. Chem. Soc.* **1996**, *118*, 8266.

Received July 03, 2014