Designing New α,β-Unsaturated Thioesters for the Catalytic, Enantioselective *Friedel–Crafts* Alkylation of Indoles

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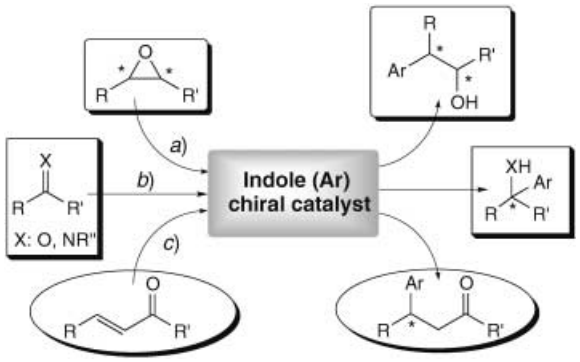
Dedicated to Professor *Duilio Arigoni* on the occasion of his 75th birthday

A new class of α,β-unsaturated *S*-(1,3-benzoxazol-2-yl) thioesters of type **2** have been synthesized and effectively employed as electrophiles in the stereoselective alkylation of indoles. The combination of electronic as well as steric properties of such *Michael* acceptors allowed us to carry out *Friedel–Crafts* alkylations of various substituted indoles in the presence of a catalytic amount (20 mol-%) of chiral cationic [Pd^{II}(Tol-binap)] complexes. With the optimized catalytic system ($PdCl_2(MeCN)_2$/Tol-binap/$AgSbF_6$), the desired β-indolyl-substituted thioderivatives **4** were obtained in good yield, with an enantiomeric excess (ee) of up to 86%. The remarkable versatility of the enantiomerically enriched thioesters **4** was demonstrated by quantitatively transforming them into optically active β-indolyl esters and amides under mild conditions. With this stereoselective, catalytic *Friedel–Crafts* reaction, we open up the way towards new α,β-unsaturated compounds that could be suitable candidates for the preparation of a number of optically active β-substituted carboxylic compounds.

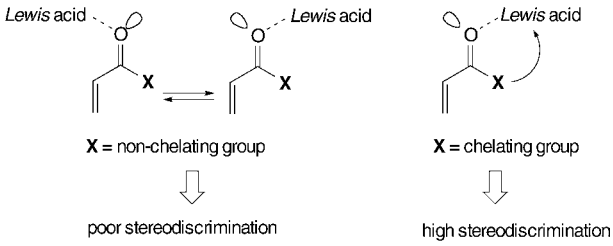
Introduction. – *Friedel–Crafts* (*FC*) alkylation represents one of the most valuable routes to the synthesis of aromatic compounds. Since the early days of *FC* chemistry (large excess of *Lewis* acids, scarce regioselectivity, low yields), remarkable modifications have been introduced towards milder and environmentally more-friendly procedures. In particular, homogenous as well as heterogenous catalytic protocols have received growing attention over the past years [1]. Pioneering stereoselective *FC* alkylations of electron-rich aromates with carbonyl compounds and epoxides, in the presence of chiral organic or organometallic catalysts, were recently reported to proceed with high levels of stereocontrol [2]. Among aromatics, of particular relevance is the indole framework '*…identified as a privileged structure* […] *with representation in over 3000 natural isolated and 40 medicinal agents in diverse therapeutic action*' [3]. The literature covering the asymmetric catalytic alkylation of indoles is extensive, and several approaches, namely ring-opening of enantiomerically pure epoxides [4], 1,2-addition to carbonyls [5], and *Michael*-type addition to α,β-unsaturated compounds [3][6] were effectively adopted to control the stereochemical outcome of the reaction (*Scheme 1*). In this context, we recently described the first highly enantioselective addition of indoles to α,β-unsaturated aryl ketones in the presence of a chiral [salen·AlCl]/base complex as the catalyst [7]. As a part of our ongoing studies, we decided to investigate an analogous process with more-challenging *carboxylic* acid derivatives. Both the large presence of enantiomerically enriched β-indolyl-substituted carboxylic fragments in natural compounds [8] and their relatively difficult syntheses (starting

from differently functionalized derivatives) explain the high interest of the chemical community in this research field[1]). However, all the stereoselective protocols reported so far require the use of bidentate substrates to guarantee high stereodiscrimination (*Scheme 2*). This condition can represent a structural limitation, especially when the ancillary fragments are hard to remove from the final product.

Scheme 1. *Possible Approaches in the Asymmetric* Friedel–Crafts *Alkylation of Indoles. a*) Ring opening of enantiomerically pure epoxides; *b*) 1,2-addition to carbonyl compounds; *c*) *Michael*-type addition to α,β-unsaturated compounds.



Scheme 2. *Lone-Pair Discrimination Based on* Lewis *Acid–Carbonyl-Compound Interaction.* The process is generally nonselective for monodentate substrates. Highly selective interactions are often observed with bidentate compounds.



Here, we describe the synthesis and characteristics of a new class of easy-to-handle, reactive, α,β-unsaturated, tailored *S*-(1,3-benzoxazol-2-yl) thioesters and demonstrate their versatility in a new enantioselective *FC* alkylation of indoles catalyzed by cationic [Pd^{II}(Tol-binap)] (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene) complexes.

Results and Discussion. – Frequently, during the modular design of α,β-unsaturated carboxylic-type *Michael* acceptors, the incorporation of an additional tailored auxiliary (**A**) at the C=O moiety helps controlling both the chemo- and stereoselectivity of subsequent transformations (*Fig. 1*). The properties of an ideal ancillary framework are

[1]) At present, some β-indolyl esters and β-indolyl aldehydes are commercially available in enantiomerically pure form [9].

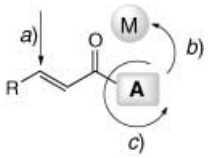
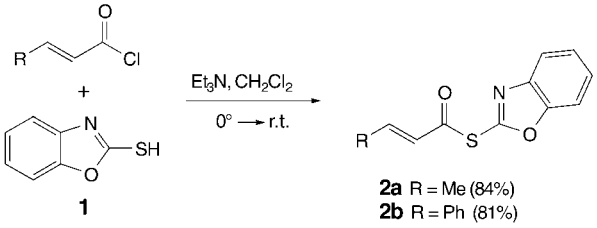


Fig. 1. *Requirements for auxiliaries* (**A**) *in 1,4-conjugate additions. a*) Electrophilic enhancement; *b*) coordinating group; *c*) facile introduction/removal.

well-known: *a*) it must enhance the electrophilicity at the β-position; *b*) it must include suitable functional groups capable of coordinating to the metal center of a *Lewis* acid (usually, five- and six-membered rings are highly effective in obtaining rigid complex conformations), and *c*) it must be easy to introduce into the starting material, easy to remove from the product, and possibly recoverable.

To this purpose, we decided to investigate commercially available and inexpensive 2-sulfanylbenzoxazole (=1,3-benzoxazole-2-thiol; **1**) as an auxiliary of α,β-unsaturated carboxylic compounds. Surprisingly, heteroaromatic thiols of type **1**, although commonly used as coupling agents in peptide synthesis and in the functionalization of pharmacologically active compounds[2]), have not been used so far as ancillary fragments in chemo- and stereoselective processes. Upon condensation of (*E*)-crotonyl and (*E*)-cinnamyl chloride with **1** (*Scheme 3*), *S*-(1,3-benzoxazol-2-yl) (*E*)-but-2-enethioate (**2a**) and *S*-(1,3-benzoxazol-2-yl) (*E*)-3-phenylprop-2-enethioate (**2b**) were isolated in high yields after recrystallization or flash chromatography (84% and 81%, resp.). The products were isolated as white (**2a**) and yellow (**2b**) air-stable solids that can be stored for long time without decomposition.

Scheme 3. *Synthesis of* α,β*-Unsaturated* S*-Acyl Sulfanyl-1,3-benzoxazoles.* The α,β-unsaturated thioesters **2a**,**b** can be prepared in high yields by direct condensation of heteroaromatic thiol **1** with the desired acyl chloride.

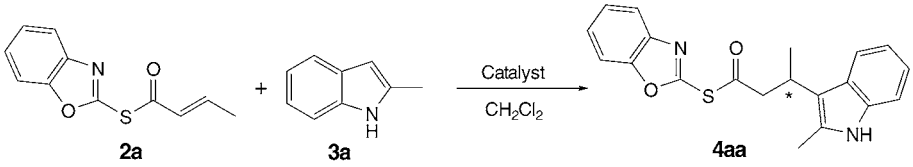


In continuation of our ongoing studies on new catalytic and enantioselective *FC Michael*-type reactions of indoles, the activity of **2a** as an alkylating agent for 2-methyl-1*H*-indole (**3a**) was examined in the presence of a range of chiral catalysts. The data collected in *Table 1* show that chiral complexes of late transition metals (Cu, Pd) are more promising as catalysts than Sc^{III} and Zn^{IV} systems, promoting the 1,4-addition chemoselectively[3]), and furnishing the desired β-indolyl adduct **4aa** in good yields (up to 80%) and moderate enantioselectivity (*Entries 4–6*, *Table 1*). Although the [Cu^{I}(Tol-binap)] and the [Pd^{II}(Tol-binap)] catalytic systems yielded **4aa** in comparable enantiomeric excess, the reaction with the Pd complex was significantly faster

[2]) For recent applications of **1** as a coupling reagent, see [10].

[3]) The isolated yields are remarkable due to the well-established susceptibility of *S*-acyl benzoxazoles to acylation processes in the presence of nucleophiles [11].

Table 1. *Screening of Chiral Organometallic Catalysts in the Reaction of* **2a** *with 2-Methylindole*[a])



2a **3a** **4aa**

Entry	Catalyst ([mol-%])[b])	*t* [h]	Yield [%][c])	ee [%][d])
1	binam($Bn)_2$/$Sc(OTf)_3$ (20)	20	80	0
2	binol/Et_2AlCl (10)	20	80	14
3	box($Ph)_2$/$Zn(OTf)_2$ (10)	20	55	12
4	binap/$Cu(OTf)_2$ (20)	20	40	36
5	Tol-binap/$CuPF_6$ (20)	20	72	57
6	Tol-binap/$(MeCN)_2PdCl_2$/2 $AgSbF_6$ (20)	2	80	56

[a]) All reactions were carried out in anh. CH_2Cl_2 at r.t. The catalysts were made *in situ.* [b]) binam = *N*,*N*′-dibenzyl-1,1′-binaphthyl-2,2′-diamine; binol = 1,1′-binaphthyl-2,2′-diol; box($Ph)_2$ = 2,2′-methylene bis[4,5-diphenyl-2-oxazoline]; binap: 2,2′-(diphenylphosphino)-1,1′-binaphthyl; Tol-binap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl. [c]) Isolated yields after chromatographic purification. [d]) Determined by chiral HPLC analysis of the benzylamide derivative (see *Exper. Part*).

(consumption of the starting material in 2 *vs.* 20 h). This aspect prompted us to optimize the catalytic protocol with the chiral cationic [Pd^{II}(Tol-binap)] complexes.

It is noteworthy that, despite the enormous impact of Pd in cross-coupling reactions, the activity of Pd-based, cationic, chiral *Lewis* acids has been explored only in a limited number of reactions[4]); and no examples of asymmetric Pd-catalyzed *FC* processes have been reported to date.

After our initial attempts to optimize the *FC* conditions, the chiral cationic Pd^{II}-bisphosphine catalyst **5** was conveniently prepared *in situ* by dissolving commercially available $PdCl_2(MeCN)_2$ (1 equiv.) and (*S*)-Tol-binap (1 equiv.) in toluene, followed by exchange reaction with $AgSbF_6$ (2 equiv.) in the solvent of choice (*Scheme 4*) [12][5]). An initial solvent screening in the *FC* reaction of **2a** with **3a** revealed that MeCN and EtCN afforded the highest chemical and optical yields of **4aa** (ee 73–77%; *Entries 3* and *4*, *Table 2*). However, the use of MeCN gave rise to *ca.* ten-times faster reaction rates. On the other hand, more strongly coordinating solvents such as DMF caused the complete failure of the reaction (*Entry 5*, *Table 2*).

The cationic [Pd^{II}(Tol-binap)]$(BF_4)_2$ complex [13] was, for comparison, isolated, following a known procedure, and tested in the *FC* reaction. In this case, **4aa** was isolated with comparable enantioselectivity (ee 75%), but the yield dropped to 50% (*Table 2*, *Entry 6*) compared to the *in situ* procedure. Furthermore, several AgX salts were tested ($AgBF_4$, AgOTf, $AgPF_6$), but the stereochemical outcome was similar to

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4) *Diels–Alder* reactions [12a], aldol reactions [12b,c], 1,3-dipolar cycloadditions [12d], *Michael* reactions involving chiral enolates [12e], and hydroaminations [12f,g].

5) The insoluble AgCl formed during the exchange reaction did not significantly affect the outcome: comparable levels of chemical and optical yields of **4aa** were, in fact, obtained, when the insoluble Ag salt was removed before adding the reagents.

Scheme 4. *Schematic Representation of the* in situ *Preparation of the Catalyst.* The isolated chiral Pd complex promoted the enantioselective alkylation with comparable stereocontrol.

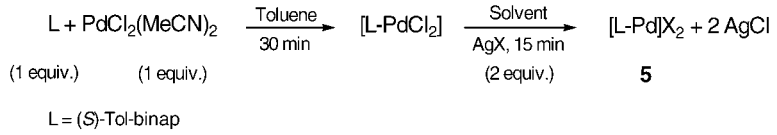

Table 2. *Optimization of the Catalytic Asymmetric Addition of 2-Methylindole to* **2a** *in the Presence of [Pd^{II}/Tol-binap/2 AgX] Prepared* in situ

Entry	Solvent	AgX	*t* [h]	*T* [°]	Yield [%][a])	ee [%][b])
1	CH_2Cl_2	$AgSbF_6$	2	r.t.	80	56
2	THF	$AgSbF_6$	2	r.t.	70	73
3	MeCN	$AgSbF_6$	2	r.t.	80	73
4	EtCN	$AgSbF_6$	20	r.t.	80	77
5	DMF	$AgSbF_6$	20	r.t.	0	–
6	MeCN	$AgSbF_6$	2	r.t.	50	75[c])
7	MeCN	$AgPF_6$	2	r.t.	72	72
8	MeCN	AgOTf	2	r.t.	79	71
9	MeCN	$AgBF_4$	2	r.t.	80	72
10	MeCN	$AgSbF_6$	16	0	75	80
11	MeCN	$AgSbF_6$	40	– 30	70	82

[a]) Isolated yields after chromatographic purification. [b]) Determined by chiral HPLC analysis of the *N*-benzylamide derivative (see *Exper. Part*). [c]) The reaction was carried out with *isolated* [Pd(Tol-binap)] complex as catalyst.

that obtained in the reaction with $AgSbF_6$ (*Table 2*, *Entries 7–9*)[6]). Finally, the effect of the temperature on the stereochemical outcome of the process was evaluated (*Entries 10* and *11*). By running the model *FC* alkylation at – 30°, **4aa** was isolated in 82% ee (*Entry 11*) instead of 80% ee (*Entry 10*), which lies within experimental error. Under optimal conditions, indole **3a** was also reacted with the cinnamic acid derivative **2b** in the presence of 20 mol-% of catalyst. However, **2b** showed only scarce reactivity, providing **4ba** in good enantiomeric excess (78%), but in low yield (35%)[7]).

Next, we investigated *Michael*-type additions of a range of indoles (**3b–g**) to the electrophile **2a** (*Table 3*). The stereoselectivity was generally good (ee 70–86%), and satisfactory yields were obtained with indoles **3b**, **3d**, and **3e**. However, the hetero-substituted indoles **3c**, **3f**, and **3g** provided the desired 1,4-adducts in lower yields (*Table 3*, *Entries 3*, *6*, and *7*). Remarkable is the ee obtained with 1*H*-indole proper (**3b**). In fact, by carrying out the catalytic conjugate addition at 0°, **4ab** was isolated in 53% yield and 85% ee (*Table 3*, *Entry 2*).

The absolute configurations of the *Michael* adducts were determined as (*R*) by chemical correlation. To this aim, **4ab** (ee 78%) was converted into the known methyl

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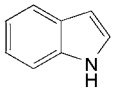
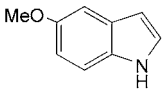
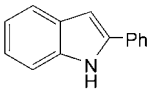
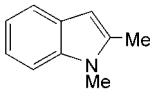
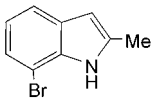
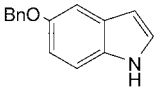
6) The isolated [Pd^{II}(Tol-binap)(H_2O)$_2$] complex did not catalyze the reaction under these conditions.

7) The use of the analogous 2-sulfanylbenzothiazole as an ancillary fragment has been taken into account as well. However, the corresponding *S*-crotonyl derivative is air-sensitive and, when reacted with **3a** under optimal conditions, the desired *β*-indolyl adduct was formed only in modest chemical and optical yields (22 and 42%, resp.).

Table 3. *Catalytic Asymmetric Addition of Indoles to* **2a** *Catalyzed by* **5** (20 mol-%)

Entry[a])	*t* [h]	Indole	Product	Yield [%][b])	ee [%][c])	Config.[d])
1	18	 **3b**	**4ab**	80	78	(*R*)
2	72		**4ab**	53	85[e])	(*R*)
3	18	 **3c**	**4ac**	20[f])	77	(*R*)
4	24	 **3d**	**4ad**	50	86	(*R*)
5	18	 **3e**	**4ae**	70	70	(*R*)
6	20	 **3f**	**4af**	32[f])	79	(*R*)
7	72	 **3g**	**4ag**	35[g])	86	(*R*)

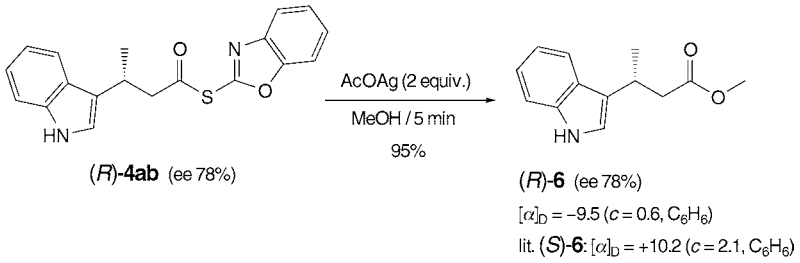
[a]) Reactions were carried out in anh. CH_2Cl_2 at r.t. [b]) Isolated yields after chromatographic purification. [c]) Determined by chiral HPLC of the *N*-benzylamide derivative (see *Exper. Part*). [d]) The abs. configurations of the 1,4-adducts were assumed to be (*R*) by considering an analogous approaching trajectory to the activated electrophile for *all* the indoles. [e]) The reaction was performed at 0°. [f]) Presence of by-products. [g]) Unreacted starting material (51%) was recovered after chromatographic purification.

ester **6** with AcOAg in MeOH (*Scheme 5*), and its optical rotational ((*R*)-**6**: ee 78%, $[\alpha]_D = -9.5$ ($c = 0.6$, C_6H_6)) was compared with an authentic, enantiomerically pure sample [14].

The absolute configuration determined can be understood by envisaging a bidentate six-membered coordination of **2a** to the [Pd^{II}((*S*)-Tol-binap)] complex in analogy to previously reported studies [10]. In *Fig. 2*, a tentative approaching trajectory of the indole to **2a** coordinated with the Pd catalyst is depicted. Here, one of the tolyl groups of the chiral ligand preferentially shields the *Si*-face of **2a**, justifying the experimentally established absolute configuration of **4ab**[8]).

[8]) The two-site-binding interaction between substrate and catalyst is crucial to guarantee reactivity as well as stereocontrol. In fact, when the reaction was carried out with mono-cationic chiral [Pd^{II}(Tol-binap)(H_2O)], or when the monodentate compound *S*-(2-naphthyl) (*E*)-but-2-enethioate was reacted with **3a**, no reaction occurred.

Scheme 5. *Determination of the Absolute Configuration of the* Michael *Adducts* **4**. Enantiomerically enriched **4ab** was converted into the known methyl ester **6** with AcOAg at room temperature.



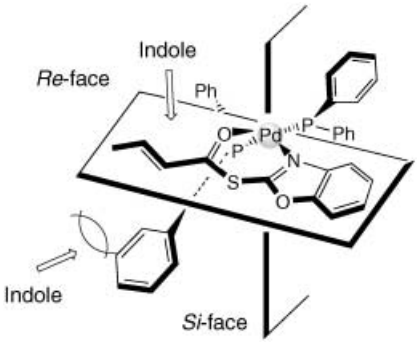


Fig. 2. *Hypothetic trajectory of the incoming indole during the enantiodiscriminating step*. The asymmetric induction observed in the reaction can be razionalized by considering a two-site-binding interaction between the Pd catalyst and the substrate.

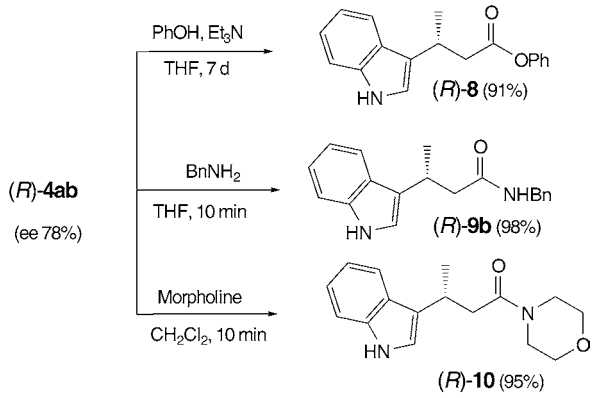
Based on the well-known affinity of indole rings to cationic *Lewis* acids (metals) [15][9]), we investigated a double activation mechanism (coordination/activation of the electrophile by the Pd complex, and enhancement of the reactivity of the indole through the interaction with the metal center). However, the absence of a detectable non-linear effect [17] in the reaction between **2a** and 2-methyl-1*H*-indole (**3a**) ruled out such a hypothesis.

The remarkable synthetic utility of compounds of type **4** was further demonstrated by the easy handling of the enantiomerically enriched (*R*)-**4ab** (ee 78%), which was promptly converted into the phenyl ester **8** [11], into the *N*-benzyl amide **9b**, and into the morpholine amide **10** in high yields (91, 98, and 95%, resp.) and without racemization (*Scheme 6*). The mild experimental conditions and the possibility of recovering the starting thioester during chromatographic purification speak for the versatility of our procedure.

Conclusions. – The introduction of a sulfanyl-1,3-benzoxazole unit into α,β-unsaturated carboxylic compounds renders them suitable electrophiles for stereoselective *Friedel–Crafts* alkylations of indoles in the presence of the [Pd^{II}(Tol-binap)] complex as the catalyst. The enantiomerically enriched 1,4-adducts obtained represent valuable synthetic intermediates for the preparation of a range of key building blocks bearing asymmetric centers adjacent to the heteroaromatic system. Further studies

9) For addition compounds between indoles and *Lewis* acids, see [16].

Scheme 6. *Synthetic Versatility of Adduct* **4ab**



addressed toward the preparation of thio-compounds in different asymmetric transformations are currently in progress.

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Experimental Part

General. Flash-column chromatography (FC) was performed on silica gel *60* (270–400 mesh). All commercially available indoles (*Aldrich*) were used as received. Anal. HPLC (high-performance liquid chromatography): HPLC-grade i-PrOH and hexane as eluting solvents, *Daicel Chiralcel*^{TM}*-OD* column (0.46 × 25 cm i.d.; *Daicel, Inc.*), detection with a variable-wavelength UV detector (deuterium lamp, 190–600 nm). Melting points (m.p.) are uncorrected. Optical rotations ($[\alpha]_D$) were determined in a 1-ml cell with a path length of 10 mm. FT-IR Spectra (neat): in cm^{-1}. ^{1}H-NMR Spectra: chemical shifts δ in ppm rel. to $SiMe_4$ as internal standard, coupling constants J in Hz. ^{13}C-NMR Spectra: proton-decoupling mode, chemical shifts δ in ppm, $CDCl_3$ (δ 77.0 ppm) as the internal standard (rel. to $SiMe_4$). GC/MS Spectra: EI mode (70 eV), with GC injection; in *m*/*z* (rel. intensity). Elemental analyses were carried out with a CHNOS analyzer.

Preparation of the α,β-Unsaturated S*-(1,3-Benzoxazol-2-yl) Thioesters* **2**. To a cold soln. (0°) of 1,3-benzoxazole-2-thiol (1.51 g, 10 mmol) and Et_3N (1.53 ml, 11 mmol) in CH_2Cl_2 was added dropwise a soln. of (*E*)-acyl chloride (11 mmol) in CH_2Cl_2. The mixture was allowed to warm to r.t., stirred for 2 h, quenched with sat. aq. $NaHCO_3$ soln., and extracted with Et_2O. The combined org. layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the dark-yellow solid was purified by recrystallization (hexane) or by FC.

S*-(1,3-Benzoxazol-2-yl) (*E*)-But-2-enethioate* (**2a**). Yield: 84%. White solid. M.p. 89–91°. IR (nujol): 2923, 2853, 1699, 1639, 1461, 1354, 1241, 1135, 1089, 744. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.94–7.87 (*m*, 1 H); 7.63–7.55 (*m*, 1 H); 7.42–7.28 (*m*, 4 H); 2.08 (*dd*, J = 6.9, 1.5, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 179.2; 165.8; 149.4; 147.2; 130.4; 126.1; 125.7; 124.2; 115.5; 110.1; 18.9. EI-MS: 219 (11, M^+), 191 (14), 151 (11), 122 (12), 69 (100). Anal. calc. for $C_{11}H_9NO_2S$ (219.0): C 60.26, H 4.14 N 6.39; found: C 60.24, H 4.11, N 6.37.

S*-(1,3-Benzoxazol-2-yl) (*E*)-3-Phenylbut-2-enethioate* (**2b**). FC (cyclohexane/CH_2Cl_2 9:1). Yield: 81%. Yellow solid. M.p. 156–158°. IR (nujol): 3078, 2945, 2851, 2720, 1686, 1606, 1459, 1373. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.23 (*d*, J = 15.3, 1 H); 7.95–7.02 (*m*, 2 H); 7.65–7.22 (*m*, 2 H); 7.43–7.41 (*m*, 3 H); 7.30–7.28 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.4; 165.3; 147.0; 146.4; 133.8; 130.8; 129.5; 128.6; 128.4; 125.4; 125.0; 118.3; 115.1; 10.9. EI-MS: 281 (8, M^+), 253 (4), 131 (100), 103 (78), 77 (60), 51 (14). Anal. calc. for $C_{16}H_{11}NO_2S$ (281.1): C 68.31, H 3.94 N 4.98; found: C 68.28, H 3.91, N 4.97.

General Procedure for Enantioselective FC *Alkylations*. In a dried, two-neck flask, $PdCl_2(MeCN)_2$ (5.2 mg, 0.02 mmol) and Tol-binap (13.6 mg, 0.02 mmol) were suspended in anh. toluene (0.5 ml). The orange mixture was stirred for *ca.* 30 min, until a bright-yellow precipitate formed. The solvent was removed under reduced

pressure, and anh. MeCN was added (2.0 ml). To the resulting yellow soln. was added $AgSbF_6$ (13.8 mg, 0.04 mmol), and the precipitation of AgCl was observed. After 15 min of stirring, **2a** or **2b** (0.1 mmol) and the indole (**3a**–**g**) (0.2 mmol) were added, and the mixture was stirred for the time reported in *Table 3*. The reaction was quenched with sat. aq. $NaHCO_3$ soln. and extracted with AcOEt. The org. layers were collected, dried (Na_2SO_4), and evaporated under reduced pressure. The desired β-indolyl thioester **4** was obtained by FC of the crude mixture. Further derivatization was performed as follows. To a soln. of **4** in THF, $BnNH_2$ (1.1 equiv.) was added, and the soln. was stirred for 10 min. After evaporation of the solvent, the corresponding *N*-benzyl amides **9** were obtained in quant. yield without racemization.

S-*(1,3-Benzoxazol-2-yl)* (R)*-3-(2-Methyl-1*H*-indol-3-yl)butanethioate* (**4aa**). Yield: 80% (ee 73%). White solid. R_f 0.3 (cyclohexane/Et_2O 4:1). $[\alpha]_D = +8.8$ ($c = 1.8$, $CHCl_3$). IR (nujol): 3388, 2917, 2726, 1707, 1507, 1459, 1376, 1138, 932, 738. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.91–7.80 (*m*, 1 H); 7.79–7.62 (*m*, 2 H); 7.38–7.19 (*m*, 4 H); 7.18–7.02 (*m*, 2 H); 4.22–3.74 (*m*, 3 H); 2.44 (*s*, 3 H); 1.56 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.7; 173.1; 146.4; 135.4; 130.6; 129.9; 126.9; 125.8; 125.2; 120.8; 119.2; 118.9; 115.8; 114.3; 110.3; 109.5; 45.6; 27.5; 21.0; 12.1. Anal. calc. for $C_{20}H_{18}N_2O_2S$ (350.4): C 68.55, H 5.18, N 7.99; found: C 68.52, H 5.13, N 7.97.

(R)*-3-(2-Methyl-1*H*-indol-3-yl)*-N-*(phenylmethyl)butanamide* (**9a**). Orange oil. HPLC (i-PrOH/hexane 1:9, 0.7 ml/min): t_R 47.8 min (*R*), 63.1 min (*S*). IR (neat): 3396, 3290, 3065, 2912, 2841, 1653, 1527, 1460, 1361, 1261, 780. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.83–7.52 (*m*, 2 H); 7.33–6.98 (*m*, 6 H); 6.91–6.68 (*m*, 2 H); 5.39 (br. *s*, 1 H); 4.35 (*dd*, $J = 15.0$, 6.6, 1 H); 4.09 (*dd*, $J = 15.0$, 4.8, 1 H); 3.68–3.44 (*m*, 1 H); 2.84–2.61 (*m*, 2 H); 2.29 (*s*, 3 H); 1.49 (*d*, $J = 7.4$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.4; 138.1; 135.7; 131.1; 128.4; 127.3; 127.1; 124.9; 120.8; 119.1; 118.8; 114.2; 110.6; 44.2; 43.3; 29.1; 21.2; 11.8.

S-*(1,3-Benzoxazol-2-yl)* (R)*-3-(1*H*-Indol-3-yl)butanethioate* (**4ab**). Yield: 80% (ee 78%). Yellow oil. R_f 0.3 (cyclohexane/Et_2O 3:1). $[\alpha]_D = +30.4$ ($c = 0.56$, $CHCl_3$). IR (nujol): 3416, 2952, 2919, 2853, 1732, 1474, 1454, 1348, 1248, 1012. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.16 (br. *s*, 1 H); 8.03–7.49 (*m*, 1 H); 7.78–7.64 (*m*, 2 H); 7.49–6.98 (*m*, 5 H); 6.62–6.55 (*m*, 1 H); 4.08–3.85 (*m*, 3 H); 1.55 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 178.1; 173.3; 145.9; 135.8; 131.0; 129.9; 126.7; 125.8; 125.2; 120.6; 119.1; 118.8; 115.7; 113.9; 110.3; 109.5; 45.5; 27.6; 21.1. Anal. calc. for $C_{19}H_{16}N_2O_2S$ (336.4): C 67.84, H 4.79, N 8.33; found: C 67.08, H 4.76, N 8.32.

(R)*-3-(1*H*-Indol-3-yl)-*N-*(phenylmethyl)butanamide* (**9b**). Viscous yellow oil. HPLC (i-PrOH/hexane 4:1, 0.7 ml/min): t_R 20.0 min (*S*), 25.3 min (*R*). IR (neat): 3396, 3117, 2733, 1646, 781. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.09 (br. *s*, 1 H); 7.72–7.63 (*m*, 1 H); 7.42–7.05 (*m*, 7 H); 7.01–6.90 (*m*, 2 H); 5.54 (br. *s*, 1 H); 4.31–4.24 (*m*, 2 H); 3.71–3.50 (*m*, 1 H); 2.79–2.42 (*m*, 2 H); 1.46 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.9; 141.0; 138.2; 136.6; 128.5; 127.6; 127.3; 122.1; 120.5; 119.4; 119.3; 11.3; 109.9; 45.1; 44.5; 28.9; 11.2.

S-*(1,3-Benzoxazol-2-yl)* (R)*-3-(5-Methoxy-1*H*-indol-3-yl)butanethioate* (**4ac**). Yield: 20% (ee 77%). Viscous yellow oil. R_f 0.3 (cyclohexane/Et_2O 7:3). $[\alpha]_D = +45.7$ ($c = 0.7$, $CHCl_3$). IR (neat): 3350, 1725, 1646, 1334, 1102, 1016. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.98–7.91 (*m*, 1 H); 7.89 (br. *s*, 1 H); 7.42–7.18 (*m*, 4 H); 7.17–7.09 (*m*, 2 H); 6.88–6.82 (*m*, 1 H); 4.12–3.95 (*m*, 2 H); 3.90 (*s*, 3 H); 3.94–3.80 (*m*, 1 H); 1.56 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 179.1; 173.4; 154.1; 131.8; 125.7; 125.5; 124.6; 121.5; 120.3; 116.4; 112.6; 112.2; 110.7; 110.3; 109.9; 101.3; 56.2; 46.5; 27.8; 21.7. Anal. calc. for $C_{20}H_{18}N_2O_3S$ (366.1): C 65.55, H 4.95, N 7.64; found: C 65.49, H 4.91, N 7.65.

(R)*-3-(5-Methoxy-1*H*-indol-3-yl)*-N-*(phenylmethyl)butanamide* (**9c**). Viscous colorless oil. HPLC (i-PrOH/hexane 4:1, 0.7 ml/min): t_R 20.0 min (*S*), 28.7 min (*R*). IR (neat): 3403, 1739, 1699, 1646, 1312, 1091, 788. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.93 (br. *s*, 1 H); 7.63–7.54 (*m*, 1 H); 7.50–7.09 (*m*, 4 H); 7.04–6.89 (*m*, 1 H); 6.89–6.75 (*m*, 2 H); 5.43 (br. *s*, 1 H); 4.54–4.21 (*m*, 1 H); 4.24–4.01 (*m*, 1 H); 3.74–3.51 (*m*, 1 H); 2.81–2.66 (*m*, 2 H); 2.40 (*s*, 3 H); 1.54 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 172.8; 131.7; 130.0; 128.5; 127.5; 125.1; 124.1; 120.7; 118.9; 112.1; 110.3; 101.3; 56.0; 41.3; 28.0; 20.7; 11.9.

S-*(1,3-Benzoxazol-2-yl)* (R)*-3-(2-Phenyl-1*H*-indol-3-yl)butanethioate* (**4ad**). Yield: 50% (ee 86%). Viscous colorless oil. R_f 0.3 (cyclohexane/Et_2O 85:15). $[\alpha]_D = -9.1$ ($c = 0.41$, $CHCl_3$). IR (nujol): 3159, 2947, 2823, 2853, 1608, 1561, 1455, 1376, 1238, 1009, 733. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.86–7.68 (*m*, 2 H); 7.65–7.5 (*m*, 2 H); 7.43–6.99 (*m*, 10 H); 4.17 (*dd*, $J = 15.4$, 6.6, 1 H); 4.08–3.89 (*m*, 1 H); 3.80 (*dd*, $J = 15.4$, 7.2, 1 H); 1.56 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.5; 172.8; 146.5; 136.2; 134.5; 132.8; 129.0; 128.7; 128.5; 127.9; 125.7; 125.1; 122.1; 120.3; 120.2; 119.7; 115.8; 115.4; 111.0; 109.5; 44.4; 26.9; 21.4. Anal. calc. for $C_{25}H_{20}N_2O_2S$ (412.1): C 72.79, H 4.84, N 6.79; found: C 72.82, H 4.85, N 6.78.

(R)*-3-(2-Phenyl-1*H*-indol-3-yl)*-N-*(phenylmethyl)butanamide* (**9d**). Viscous colorless oil. HPLC (i-PrOH/hexane 87:13, 0.7 ml/min): t_R 43.7 min (*R*), 49.9 min (*S*). IR (nujol): 3281, 2936, 2726, 1758, 1646, 1521, 1458, 1376, 1308, 1256, 1091, 741, 697. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.95 (br. *s*, 1 H); 7.78–7.72 (*m*, 1 H); 7.50–7.10 (*m*, 12 H); 6.82–6.75 (*m*, 1 H); 5.41 (br. *s*, 1 H); 4.36–4.24 (*m*, 1 H); 4.17–4.07 (*m*, 1 H); 3.84–3.75 (*m*, 1 H); 2.93 (*dd*, $J = 13.8$, 9.6, 1 H); 2.73 (*dd*, $J = 13.8$, 6.3, 1 H); 1.52 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.7;

135.6; 134.2; 132.8; 132.5; 132.0; 128.8; 128.7; 128.4; 128.0; 127.1; 122.1; 120.0; 119.7; 11.3; 103.2; 100.1; 98.9; 43.9; 43.3; 28.9; 21.8.

S-*(1,3-Benzoxazol-2-yl) (*R*)-3-(1,2-Dimethyl-1*H*-indol-3-yl)butanethioate* (**4ae**). Yield: 70% (ee 70%). Light-brown oil. R_f 0.3 (cyclohexane/Et_2O 85:15). $[\alpha]_D = +17.9$ ($c = 1.4$, $CHCl_3$). IR (neat): 3390, 2727, 1745, 1653, 1096. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.95–7.78 (*m*, 2 H); 7.57–7.11 (*m*, 6 H); 4.42–3.80 (*m*, 3 H); 3.71 (*s*, 3 H); 2.51 (*s*, 3 H); 1.56 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.7; 173.3; 146.5; 136.8; 132.5; 129.9; 125.9; 125.7; 125.1; 120.4; 119.0; 118.8; 115.6; 113.5; 109.5; 108.7; 45.7; 30.9; 29.7; 28.1; 21.3. Anal. calc. for $C_{21}H_{20}N_2O_2S$ (364.1): C 69.20, H 5.53, N 7.69; found: C 69.16, H 5.49, N 7.68.

*(*R*)-3-(1,2-Dimethyl-1*H*-indol-3-yl)-*N*-(phenylmethyl)butanamide* (**9e**). Brown oil. HPLC (i-PrOH/hexane 4:1, 0.7 ml/min): t_R 12.5 min (*S*), 15.6 min (*R*). IR (neat): 3380, 3287, 1635, 1510, 1480, 1246, 1092, 732. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.69–7.57 (*m*, 1 H); 7.42–6.90 (*m*, 7 H); 6.83–6.68 (*m*, 1 H); 5.38 (br. *s*, 1 H); 4.45–3.88 (*m*, 3 H); 3.59 (*s*, 3 H); 3.86–3.61 (*m*, 2 H); 2.27 (*s*, 3 H); 1.49 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 172.5; 138.0; 137.0; 132.9; 128.4; 127.2; 125.9; 120.4; 119.0; 118.5; 114.0; 109.0; 108.8; 44.2; 43.2; 30.9; 28.2; 21.5; 10.5.

S-*(1,3-Benzoxazol-2-yl) (*R*)-3-(7-Bromo-2-methyl-1*H*-indol-3-yl)butanethioate* (**4af**). Yield: 32% (ee 79%). Viscous colorless oil. R_f 0.3 (cyclohexane/Et_2O 4:1). $[\alpha]_D = +35.4$ ($c = 1.05$, $CHCl_3$). IR (neat): 3423, 1626, 1573, 1454, 1235, 1122. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.96–7.77 (*m*, 2 H); 7.69–7.53 (*m*, 1 H); 7.38–7.09 (*m*, 4 H); 7.04–6.88 (*m*, 1 H); 4.21–3.70 (*m*, 3 H); 2.47 (*s*, 3 H); 1.56 (*d*, $J = 7.2$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 178.7; 173.0; 146.4; 133.9; 131.6; 129.8; 128.0; 125.9; 125.3; 123.1; 120.4; 118.1; 115.8; 115.6; 109.6; 104.1; 45.5; 27.7; 21.0; 12.2. Anal. calc. for $C_{20}H_{17}BrN_2O_2S$ (428.0): C 55.95, H 3.99, N 6.52; found: C 55.91, H 3.97, N 6.51.

*(*R*)-3-(7-Bromo-2-methyl-1*H*-indol-3-yl)-*N*-(phenylmethyl)butanamide* (**9f**). Orange oil. HPLC (i-PrOH/hexane 4:1, 0.4 ml/min): t_R 30.0 min (*S*), 31.5 min (*R*). IR (nujol): 3449, 2959, 2926, 2720, 1653, 1474, 1374, 1169, 1129, 963, 718. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.93 (br. *s*, 1 H); 7.63–7.54 (*m*, 1 H); 7.50–7.09 (*m*, 4 H); 7.04–6.89 (*m*, 1 H); 6.89–6.75 (*m*, 2 H); 5.43 (br. *s*, 1 H); 4.54–4.21 (*m*, 1 H); 4.24–4.01 (*m*, 1 H); 3.74–3.51 (*m*, 1 H); 2.81–2.66 (*m*, 2 H); 2.40 (*s*, 3 H); 1.54 (*d*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 172.1; 132.1; 128.5; 127.9; 127.2; 125.0; 124.1; 123.1; 120.3; 118.0; 115.5; 110.3; 104.4; 44.1; 43.3; 29.3; 21.1; 11.9.

S-*(1,3-Benzoxazol-2-yl) (*R*)-3-[5-(Phenylmethoxy)-1*H*-indol-3-yl]butanethioate* (**4ag**). Yield: 35% (ee 86%). Viscous yellow oil. R_f 0.3 (cyclohexane/Et_2O 7:3). $[\alpha]_D = +39.9$ ($c = 1.1$, $CHCl_3$). IR (nujol): 3416, 2969, 2817, 1732, 1626, 1450, 1389, 1334, 1089, 919, 730. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.99–7.90 (*m*, 1 H); 7.83 (br., *s*, 1 H); 7.53–7.02 (*m*, 11 H); 6.96–6.89 (*m*, 1 H); 5.17–5.09 (*m*, 2 H); 4.03–3.91 (*m*, 2 H); 3.90–3.78 (*m*, 1 H); 1.50 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 178.8; 173.1; 153.0; 131.8; 128.5; 127.7; 127.6; 125.9; 125.4; 125.1; 124.2; 121.3; 120.1; 116.1; 113.0; 111.9; 110.4; 110.0; 109.6; 102.8; 71.0; 46.2; 27.5; 21.4. Anal. calc. for $C_{26}H_{22}N_2O_3S$ (442.1): C 70.57, H 5.01, N 6.32; found: C 70.52, H 4.97, N 6.34.

*(*R*)-3-[5-(Phenylmethoxy)-1*H*-indol-3-yl]-*N*-(phenylmethyl)butanamide* (**9g**). Viscous brown oil. HPLC (i-PrOH/hexane 4:1, 0.7 ml/min): t_R 26.8 min (*S*), 30.3 min (*R*). IR (nujol): 3165, 2965, 2712, 1631, 1461, 1379, 1268, 1168, 1091, 1021, 721. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.87–7.77 (*m*, 2 H), 7.62–7.11 (*m*, 10 H); 7.08–6.86 (*m*, 3 H); 5.21 (br. *s*, 1 H); 5.18–5.05 (*m*, 2 H); 4.44–4.21 (*m*, 2 H); 3.65–3.65 (*m*, 1 H); 2.51–2.41 (*m*, 2 H); 1.57 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.0; 153.0; 131.9; 128.5; 128.4; 127.7; 127.7; 127.6; 127.5; 127.5; 127.2; 126.4; 121.5; 120.2; 113.0; 112.2; 112.0; 111.9; 103.2; 71.1; 43.4; 28.9; 21.1; 11.6.

*Phenyl (*R*)-3-(1*H*-Indol-3-yl)butanoate* (**8**). Yield: 91%. Viscous yellow oil. HPLC (i-PrOH/hexane 4:1, 0.7 ml/min): t_R 11.8 min (*R*), 12.6 min (*S*). R_f 0.3 (cyclohexane/AcOEt 4:1). IR (nujol): 3363, 2965, 2919, 2853, 1653, 1507, 1454, 1261, 1001, 783. ^{1}H-NMR ($CDCl_3$, 200 MHz): 8.03 (br. *s*, 1 H); 7.42 (*d*, $J = 7.6$, 1 H); 7.48–7.05 (*m*, 7 H); 7.02–6.88 (*m*, 2 H); 3.77 (*q*, $J = 14.4$, 7.4, 1 H); 3.09 (*dd*, $J = 14.8$, 6.6, 1 H); 2.86 (*dd*, $J = 14.8$, 8.2, 1 H); 1.55 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.6; 129.3; 125.7; 125.2; 124.3; 122.1; 121.5; 120.3; 119.3; 119.2; 11.3; 110.4; 110.2; 42.5; 28.3; 21.2. Anal. calc. for $C_{18}H_{17}NO_2$ (279.1): C 77.40, H 6.13, N 5.01; found: C 77.42, H 6.09, N 5.00.

*(*R*)-3-(1*H*-Indol-3-yl)-*N*-(4*H*-1,4-oxazin-4-yl)acetamide* (**10**). Yield: 95%. White solid. HPLC (i-PrOH/hexane 4:1, 0.7 ml/min): t_R 15.9 min (*S*), 25.8 min (*R*). M.p. 161°. R_f 0.3 (cyclohexane/AcOEt 3:2). IR (nujol): 3250, 3104, 2977, 2820, 2720, 2660, 1606, 1452, 1360, 1301, 1109. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.06 (br. *s*, 1 H); 7.66 (*d*, $J = 7.8$, 1 H); 7.39–7.02 (*m*, 4 H); 3.78–3.51 (*m*, 4 H); 3.49–3.31 (*m*, 4 H); 3.49–3.08 (*m*, 2 H); 3.03–2.95 (*m*, 1 H); 1.50 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 171.0; 136.5; 126.4; 122.1; 120.9; 120.3; 119.4; 119.3; 111.3; 66.7; 46.3; 40.9; 28.6; 21.1. Anal. calc. for $C_{16}H_{20}N_2O_2$ (272.2): C 70.56, H 7.40, N 10.29; found: C 70.52, H 7.34, N 10.20.

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