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Polystyrene-Supported Cu(II)-R-Box as Recyclable Catalyst in Asymmetric Friedel–Crafts Reaction

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Abstract—The complex of copper(II) trifluoromethanesulfonate with chiral isopropyl bis(oxazoline) ligand (*i*-Pr-Box) was immobilized on accessible and inexpensive Merrifield resin according to a "click" procedure. The resulting catalyst showed high efficiency and recyclability in the asymmetric Friedel–Crafts alkylation of indole and its derivatives. The catalyst can be recycled five times without appreciable loss in activity and enantioselectivity.

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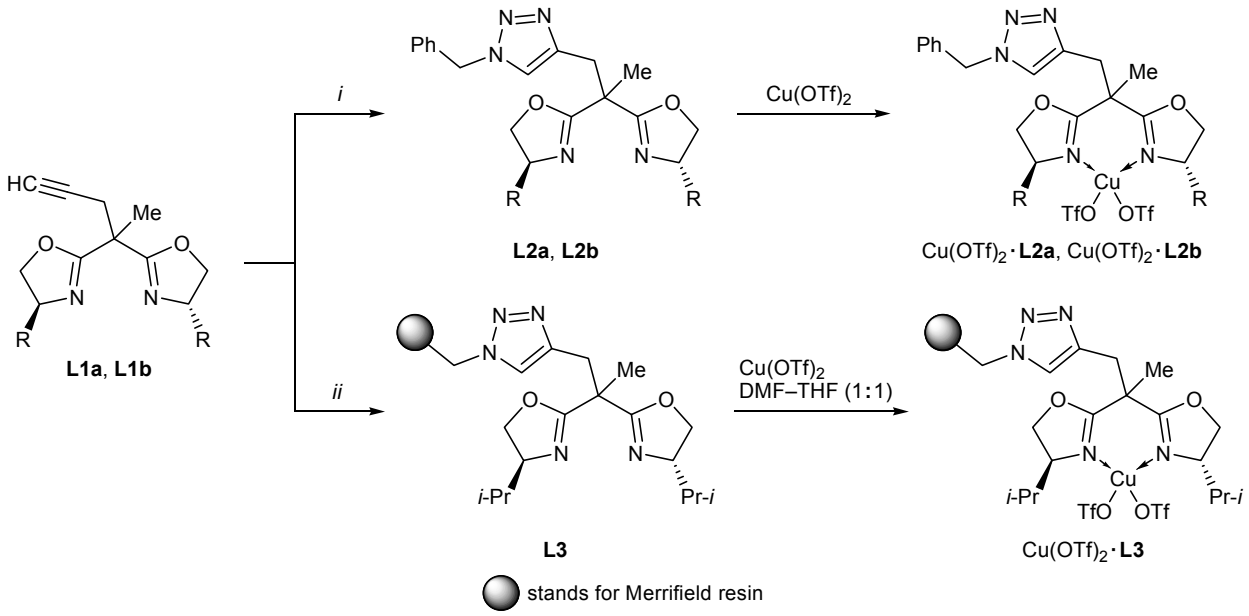
Asymmetric catalysis [1] (i.e., catalysis by transition metal complexes with chiral ligands [2], catalysis by chiral Lewis [3] or Brønsted acids [4], and organocatalysis [5]) is one of the brightest research lines in modern organic chemistry. However, large-scale application of chiral catalysts is limited by the high cost of chiral reagents, whereas metal complex catalysis involves a problem related to separation of the target products from micro impurities of heavy metals, as well as from phosphine ligands and their oxidation products [6]. The use of recyclable catalysts immobilized on soft or hard supports [7–9] makes it possible to partially solve the above problems; however, obvious advantages of such catalytic systems are often counterpoised by lowering of the reaction rate in going from homogeneous to heterogeneous conditions and by reduction of the yield and enantioselectivity.

Chiral bis(oxazoline) ligands (Box, aza-Box, Py-Box) are widely used in asymmetric organic synthesis [10–13], and their immobilization on soluble and insoluble polymers and inorganic supports makes it possible to successfully accomplish various asymmetric transformations [14, 15]. For instance, supported copper-containing bis(oxazoline) complexes were used to catalyze cyclopropanations [16–19], aziridinations [20, 21], ene reactions [22], Mukaiyama aldol condensations [23–26], and Henry and Mannich reactions [27–30]. Liu and Du [31] studied reactions of indole with nitroalkenes catalyzed by zinc complex with diphenylamine-linked bis(oxazoline) ligand immobilized onto Fréchet-type dendrimers. High yields and reproducible enantioselectivities were achieved in four catalytic cycles. Silicon dioxide- and MCM-41-supported Cu(II)-Ph-Box catalyzed the reaction of 1,3-dimethoxybenzene with methyl 3,3,3-trifluoropyruvate; however the enantioselectivity considerably decreased after reuse [32]. Aza(bisoxazoline) immobilized on a soluble poly(ethylene glycol) [22, 33] was reported to catalyze asymmetric reaction of indole with benzylidenemalonate in the presence of $Cu(OTf)_2$; however, the possibility of recycling the catalyst was not noted [34].

Jørgensen et al. [35–37] studied asymmetric Friedel–Crafts alkylation of indole with (arylmethylidene)malonates and (arylmethylidene)pyruvates in the presence of $Cu(OTf)_2$ complex with chiral *t*-Bu-Box ligand. Such reactions are of great practical importance; however, no examples of asymmetric Friedel–Crafts alkylation with the use of analogous complexes under heterogeneous conditions have been reported so far.

Supported catalysts can be obtained according to two approaches: (1) immobilization of a ligand, followed by complexation with a metal salt and (2) immobilization of a preliminarily prepared complex. Taking into account inactivity of polymeric supports toward metal salts, we selected the first approach implying ligand binding to polymeric support via copper-

Scheme 1.



R = Ph (**a**), *i*-Pr (**b**); reagents and conditions: *i*: $Cu(OAc)_2$, NaAsc, TTTA, $PhCH_2N_3$, $THF–H_2O$, 5 : 1, 20°C, 20 h; *ii*: polystyrene-N_3, CuI/TTTA, DMF–THF, 1 : 1, 60°C, 30 h.

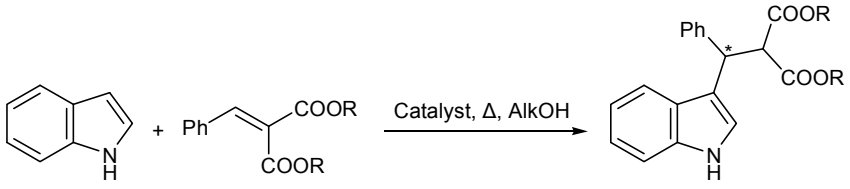
catalyzed 1,3-dipolar cycloaddition of azides to alkynes [38]. "Click" chemistry provides well studied, simple, and efficient methods for covalent binding of catalysts, including Cu-Box [15] and Cu-azaBox complexes [39, 40], to various supports.

Initially, we have synthesized in high yields (85–87%) triazoles **L2a** and **L2b** by reacting alkynyl-substituted Box-ligands **L1a** and **L1b** [41] with benzyl azide in the presence of $Cu(OAc)_2$/NaAsc/TTTA as catalytic system {TTTA is tris[(1-*tert*-butyl-1*H*-1,2,3-triazol-4-yl)methyl]amine [42]} (Scheme 1). The use of TTTA made it possible to avoid copper(II) coordination to the Box ligand. The reactions of **L2a** and **L2b** with $Cu(OTf)_2$ afforded complexes $Cu(OTf)_2 \cdot$**L2a** and $Cu(OTf)_2 \cdot$**L2b** which were used without isolation to optimize the conditions of the Friedel–Crafts reaction of indole with benzylidenemalonate (Table 1). The reactions were carried out in ethanol or isobutyl alcohol at 20 and 0°C.

The reaction catalyzed by $Cu(OTf)_2 \cdot$**L2a** (10 mol %) containing phenyl groups gave the corresponding 3-substituted indole with lower enantioselectivity (Scheme 2; Table 1, run nos. 1, 2) than in the presence of $Cu(OTf)_2 \cdot$**L2b** containing isopropyl groups (run nos. 3, 4). When $Cu(OTf)_2 \cdot$**L2a** was used as catalyst, lowering the temperature to 0°C resulted in more significant reduction of the yield than in the reaction catalyzed by $Cu(OTf)_2 \cdot$**L2b**, but the enantioselectivity increased. Therefore, the ligand containing isopropyl groups is preferred from the viewpoint of enantioselectivity. The reactions of indole (**1a**) with dimethyl and diethyl benzylidenemalonates were characterized by almost similar yields and enantioselectivities (run nos. 4, 5), whereas replacement of ethanol as solvent by isobutyl alcohol led to a slight reduction in both yield and enantioselectivity (run no. 6).

Thus, the complex $Cu(OTf)_2 \cdot$**L2b** showed high efficiency in the catalytic alkylation of indole. The ob-

Scheme 2.



1a **2a**, **2b** **3a**, **3b**

R = Et (**a**), Me (**b**).

Table 1. Reaction of indole with benzylidenemalonates catalyzed by copper(II) complexes[a]

Run no.	Compound no.	Catalyst	Solvent, temperature	Reaction time, h	Product	Yield, %	*ee*, %
1	**2a**	$Cu(OTf)_2$·**L2a**	EtOH, 20°C	24	**3a**	85	53
2	**2a**	$Cu(OTf)_2$·**L2a**	EtOH, 0°C	48	**3a**	68	54
3	**2a**	$Cu(OTf)_2$·**L2b**	EtOH, 20°C	20	**3a**	92	83
4	**2a**	$Cu(OTf)_2$·**L2b**	EtOH, 0°C	24	**3a**	88	89
5	**2b**	$Cu(OTf)_2$·**L2b**	EtOH, 0°C	24	**3b**	89	86
6	**2b**	$Cu(OTf)_2$·**L2b**	*i*-BuOH, 0°C	24	**3b**	83	83

[a] Reaction conditions: indole **1a**, 1.2 mmol; benzylidenemalonate **2**, 1 mmol; catalyst, 10 mol %; ethanol, 4 mL.

tained *ee* values indicated that the triazole substituent in **L2b** does not compete for coordination to the metal and hence does not hamper the reaction. In view of the aforesaid, in the second stage of our study ligand **L1b** was immobilized onto polystyrene (Merrifield resin).

Unlike "click" reactions of ligands **L1a** and **L1b** with benzyl azide, the reaction with azidomethylpolystyrene required more severe conditions (DMF–THF, 1:1; 60°C, 30 h; Scheme 1). The progress of the reaction was monitored by IR spectroscopy, following the disappearance of the N_3 stretching band at 2094 cm^{-1} and appearance of the C=N band at 1658 cm^{-1}. The subsequent treatment of polymer-supported *i*-Pr-Box (**L3**) with copper(II) trifluoromethanesulfonate afforded the target catalyst $Cu(OTf)_2$·**L3**. The concentration of copper therein (~0.5 mmol/g) was determined by inductively coupled plasma mass spectrometry (ICP-MS).

In the reaction of indole with diethyl benzylidenemalonate in the presence of 10 mol % of $Cu(OTf)_2$·**L3** in ethanol, the yield of the alkylation product was 74% (*ee* 87%) (Table 2, run no. 1), which is comparable with the result obtained with $Cu(OTf)_2$·**L2b** as catalyst (Table 1, run no. 4). The reaction catalyzed by $Cu(OTf)_2$·**L3** (Table 2, run no. 1) under the same conditions was expectedly much slower than under homogeneous conditions using $Cu(OTf)_2$·**L2b** (Table 1, run no. 4), and seven days against one was necessary to attain a comparable yield in the case of heterogeneous catalyst. The observed reduction of the reaction rate is a common drawback of all heterogeneous reactions since localization of reaction sites on a polymeric support considerably diminishes their accessibility for reagents residing in solution.

The catalytic efficiency of $Cu(OTf)_2$·**L3** in asymmetric Friedel–Crafts alkylation in different solvents was studied (Table 2). The best yields were obtained in methylene chloride and 1:1 ethanol–tetrahydrofuran mixture (run no. 2–4). High enantioselectivity (82–93% *ee*) was reached at –30°C in all the examined solvents except for toluene; in particular, the *ee* value of the alkylation product after recrystallization was 99% when the reaction was carried out in EtOH–THF (1:1) (run no. 3). It is quite probable that only highly accessible catalytic sites are active at low temperature, whereas those located more deeply inside a randomly packed cross-linked polymer are merely inaccessible. Nevertheless, prolonged reaction without stirring afforded a high yield and enantioselectivity. The polystyrene resin used in nonpolar solvents remained swollen even at such low temperatures.

Unlike the homogeneous reaction catalyzed by $Cu(OTf)_2$–*i*-Pr-Box [43, 44], the steric configuration of the product did not change in going from ethanol to

Table 2. Optimization of the conditions for the synthesis of diethyl (*S*)-2-[(1*H*-indol-3-yl)(phenyl)methyl]malonate (**3a**) from indole (**1a**) and diethyl benzylidenemalonate (**2a**) in the presence of $Cu(OTf)_2$·**L3**[a]

Run no.	Solvent, temperature	Reaction time, day	Yield, %	*ee*, %
1	EtOH, 0°C	7	74	87
2	EtOH–THF (1:1), 0°C	7	76	87
3	EtOH–THF (1:1), –30°C	21	83	92 >99[b]
4	CH_2Cl_2, –30°C	21	91	87
5	Acetone, –30°C	21	66 (93)[c]	93
6	EtOAc, –30°C	21	31 (68)[c]	82
7	PhMe, –30°C	21	25 (71)[c]	64
8	MeCN, –30°C	21	25 (83)[c]	87

[a] Reaction conditions: **1a**, 1.2–2 mmol (1.2–2 equiv); **2a**, 1 mmol; catalyst, 10 mol %; solvent, 4 mL.

[b] After recrystallization from ethanol.

[c] Calculated on the reacted **2a**.

Table 3. Recycling of the catalyst $Cu(OTf)_2 \cdot$ **L3** in the reaction of indole (**1a**) with diethyl benzylidenemalonate (**2a**)[a]

Cycle no.	1	2	3	4	5
Yield, %	83	71	72	74	73
ee, %	92 (>99[b])	91	92	92	92

[a] Reaction conditions: **1a**, 2 mmol; **2a**, 1 mmol; catalyst, 10 mol %; THF–EtOH (1 : 1), 4 mL; –30°C, 21 days.
[b] After recrystallization from ethanol.

methylene chloride. In all solvents indicated in Table 2, the configuration of the target product obtained in the presence of $Cu(OTf)_2 \cdot$ **L3** was the same.

Similar enantioselectivities in different solvents suggest stability and uniformity of catalytic sites, which is very important for recycling. The heterogeneous catalyst $Cu(OTf)_2 \cdot$ **L3** can be readily separated by filtration. After washing with THF and drying, it was reused five times in the reaction of indole with diethyl benzylidenemalonate (Table 3). Reduction of the yield was observed only in the second cycle, which may be due to washout of weakly bound active catalytic sites, and the catalyst then becomes stable to repeated filtrations, washings, and dryings and shows almost constant activity and enantioselectivity in at least five cycles.

Table 4. Reaction of indoles **1a**–**1f** with arylmethylidenemalonates **2a**–**2d**[a]

Run no.	Initial reactants	Temperature, °C	Product	Yield, %	*ee*, %
1	**1a** + **2b**	–30	**3b**	58	38
2	**1b** + **2a**	–30	**3c**	73	94
3	**1b** + **2a**	0	**3c**	79	73
4	**1c** + **2a**	–30	**3d**	91	97
5	**1d** + **2a**	–30	**3e**	84	94
6	**1f** + **2a**	–30	**3f**	51	66
7	**1a** + **2c**	–30	**3g**	80	89
8	**1b** + **2c**	–30	**3h**	86	89
9	**1c** + **2c**	–30	**3i**	82	91
10	**1d** + **2c**	–30	**3j**	78	86
11	**1f** + **2c**	–30	**3k**	46	61
12	**1e** + **2c**	0	**3l**	76	87
13	**1a** + **2d**	0	**3m**	99	86
14	**1b** + **2d**	0	**3n**	69	78
15	**1e** + **2d**	0	**3o**	81	73

[a] Reaction conditions: **1**, 2 mmol; **2**, 1 mmol; $Cu(OTf)_2 \cdot$ **L3**, 10 mol %; THF–EtOH (1 : 1), 4 mL; 21 days.

The nature of substituents in the initial indole molecule (both in the benzene ring and on the nitrogen atom), as well as in the aromatic ring of the olefinic component, strongly affects the asymmetric alkylation reaction under homogeneous catalysis [45–50]. We have studied how the substituents in the 5-position of indole and in the *para* position of the phenyl group of benzylidenemalonate, as well as the *N*-methyl group in indole, affect the results of $Cu(OTf)_2 \cdot$ **L3**-catalyzed asymmetric alkylation of indole (Scheme 3, Table 4).

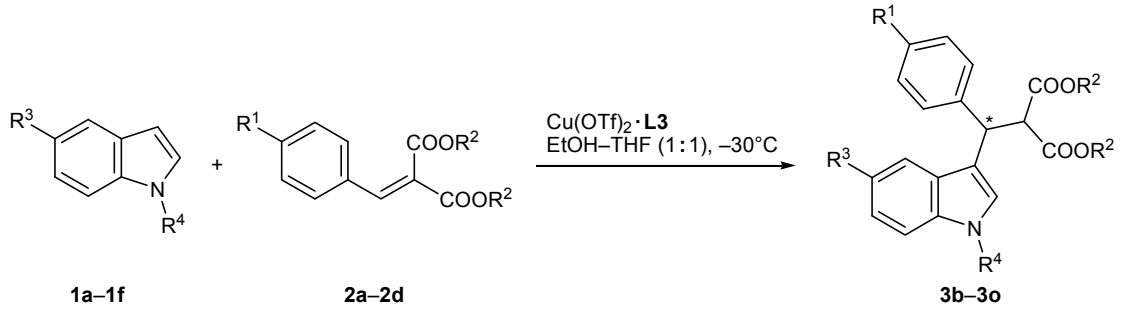
We have found that the reaction catalyzed by $Cu(OTf)_2 \cdot$ **L3** shows the same trends with respect to the substituent effects as those observed in the homogeneous catalytic reactions in the presence of $Cu(OTf)_2 \cdot$ R-Box [45–51]. Introduction of a methoxy group into the indole molecule decreased the yield but did not change the *ee* value (run no. 2). The reduced yield in the reaction with 5-methoxyindole (**1b**) may be related to its instability in the presence of Lewis acids (the reaction was accompanied by tarring, and the catalyst turned brown). The presence of a bromine atom or methyl group in the 5-position of indole (**1d** and **1c**, respectively), increased both *ee* (94 and 97%, respectively, and yield (run nos. 4 and 5).

The lowest yield and enantioselectivity (run nos. 6, 11) were obtained in the alkylation of *N*-methylindole. This may be rationalized assuming a contribution of hydrogen bonding to fixation of the reactants in the metal coordination sphere. There were no appreciable variations in the yield and enantioselectivity of the alkylation of indole and its derivatives upon introduction of a bromine atom into the *para* position of the phenyl group of benzylidenemalonate (run nos. 7–10, 12).

The reactions with diethyl 4-nitrobenzylidenemalonate **2d** were carried out at 0°C because of its poor solubility at –30°C; nevertheless, these reactions were characterized by high yields (excluding alkylation of 5-methoxyindole) and fairly high enantioselectivities (run nos. 13–15).

The catalyst $Cu(OTf)_2 \cdot$ **L3** was also tried in the reaction of indoles with a β-keto ester, namely methyl (*E*)-2-oxo-4-phenylbut-3-enoate [52, 53]. Analogous reactions under homogeneous catalysis were described in [51, 54–56]. We reacted 1 equiv of indole **1a**–**1f** with 2 equiv of methyl (*E*)-2-oxo-4-phenylbut-3-enoate (**4**) at –30 and –78°C in a 1 : 1 mixture of methanol and THF (Scheme 4, Table 5). Unfortunately, hetero-

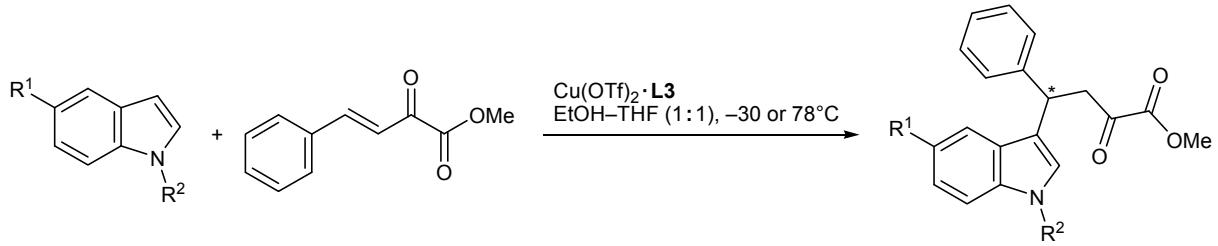
Scheme 3.



1a–1f **2a–2d** **3b–3o**

1, R^4 = H, R^3 = H (**a**), MeO (**b**), Me (**c**), Br (**d**), I (**e**); R^3 = H, R^4 = Me (**f**); **2**, R^1 = H, R^2 = Et (**a**), Me (**b**); R^2 = Et, R^1 = Br (**c**), O_2N (**d**); **3**, R^1 = R^3 = R^4 = H, R^2 = Me (**b**); R^1 = R^4 = H, R^2 = Et, R^3 = MeO (**c**), Me (**d**), Br (**e**); R^1 = R^3 = H, R^2 = Et, R^4 = Me (**f**); R^1 = Br, R^2 = Et, R^3 = R^4 =H (**g**); R^1 = Br, R^2 = Et, R^4 = H, R^3 = MeO (**h**), Me (**i**), Br (**j**); R^1 = Br, R^2 = Et, R^3 = H, R^4 = Me (**k**); R^1 = Br, R^2 = Et, R^3 = I, R^4 =H (**l**); R^1 = O_2N, R^2 = Et, R^4 = H (**m**), MeO (**n**), I (**o**).

Scheme 4.



1a–1f **4** **5a–5f**

R^2 = H, R^1 = H (**a**), MeO (**b**), Me (**c**), Br (**d**), I (**e**); R^1 = H, R^2 = Me (**f**).

geneous catalysis turned out to be much less efficient than homogeneous catalysis, primarily with respect to enantioselectivity which considerably decreased. Lowering the temperature to –78°C did not improve the results. Electron-donating methoxy and methyl groups in the initial indole (run nos. 3–6) insignificantly increase enantiomeric excess as compared to unsubstituted indole (run nos. 1, 2). 5-Bromo substitution in indole (run nos. 7, 8) favors enantioselectivity but reduces the yield. The reaction of methyl (*E*)-2-oxo-4-phenylbut-3-enoate (**4**) with *N*-methylindole (**1f**) was characterized by considerably lower enantioselectivity (30% *ee*, run no. 9).

Unexpectedly sharp increase of the yield (94%) at –78°C for methoxyindole **1b** should be noted (run no. 4), which may be related to inhibition of side processes; however, the enantioselectivity remained fairly low. Considerable increase of the enantioselectivity (from 6 to 37% *ee*) was observed in the reaction with *N*-methylindole on lowering the temperature to –78°C (run nos. 9, 10).

In summary, we were the first to accomplish asymmetric Friedel–Crafts alkylation of indoles with benzylidenemalonates under conditions of heterogeneous catalysis. The target products were obtained in up to 99% yield with up to 97% *ee*. The catalyst ensured high yield and enantioselectivity after recycling five times.

Table 5. Reaction of indoles **1a–1f** with methyl 2-oxo-4-phenylbut-3-enoate (**4**) catalyzed by $Cu(OTf)_2 \cdot$ **L3**[a]

Run no.	Indole	Temperature, °C	Product	Yield, %	*ee*, %
1	**1a**	–30	**5a**	82	34
2	**1a**	–78	**5a**	77	37
3	**1b**	–30	**5b**	68	39
4	**1b**	–78	**5b**	94	36
5	**1c**	–30	**5c**	73	39
6	**1c**	–78	**5c**	75	41
7	**1d**	–30	**5d**	79	49
8	**1d**	–78	**5d**	43	45
9	**1e**	–78	**5e**	22	30
10	**1f**	–30	**5f**	66	6
11	**1f**	–78	**5f**	68	37

[a] Reaction conditions: **1**, 1 mmol; **4**, 2 mmol; $Cu(OTf)_2 \cdot$ **L3**, 10 mol %; THF–MeOH (1 : 1), 4 mL; 27 days.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100.6 MHz, respectively, using the residual proton and carbon signals of the deuterated solvents as reference ($CHCl_3$, δ 7.26 ppm; $CDCl_3$, δ_C 77.16 ppm; DMSO-d_5, δ 2.5 ppm; DMSO-d_6, δ_C 39.52 ppm). The MALDI-TOF mass spectra (positive ion detection) were obtained on a Bruker Daltonics Ultraflex instrument using 1,8,9-trihydroxyanthracene as matrix and poly(ethylene glycols) PEG-300, PEG-400, and PEG-600 as internal standards. The IR spectra were recorded on a UR-20 spectrometer. The elemental compositions were obtained with a Vario MICRO Cube Elementar analyzer. The *ee* values were determined by chiral HPLC on a Hitachi LaChrome Elite-2000 chromatograph using a Daicel column (0.46×25 cm); the chromatograms were processed by means of MultiKhrom program. The copper content of the catalyst was determined with a Varian 720-ES ICP-OES instrument. The melting points were measured in open capillaries using an Electrothermal 9100 melting point indicator; uncorrected values are given. The purity of the isolated compounds was checked, and the progress of reactions was monitored, by TLC on Silica gel 60 F_{254} plates (Merck, Germany). The products were isolated by column chromatography on Macherey-Nagel 60 silica gel (0.040–0.063 mm) using 2.5×25-cm columns.

4,4-Bis[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pent-1-yne (**L2a**) and (4*S*,4′*S*)-2,2′-(pent-4-yne-2,2-diyl)bis(4-isopropyl-4,5-dihydro-1,3-oxazole) (**L2b**) were prepared according to the procedure described in [41]; their physicochemical constants coincided with published data.

Azidomethylpolystyrene. Chloromethyl polystyrene (*f* = 1.6 mmol/g), 6 g, was added to a solution of 8 g (123 mmol) of sodium azide in 40 mL of DMF, and the mixture was heated for 24 h at 60°C. After cooling, the mixture was filtered, and the precipitate was washed with water (400 mL), THF (200 mL), THF–MeOH (1:1; 200 mL), MeOH (200 mL), and THF (200 mL), and dried under reduced pressure at 60°C. Yield 5.74 g (96%), white powder (*f* = 1.62 mmol/g). IR spectrum (KBr): ν 2089 cm^{-1} (N_3). Found, %: C 85.51; H 7.67; N 6.82. $C_{45}H_{49}N_3$. Calculated, %: C 85.58; H 7.77; N 6.66.

"Click" reactions with benzyl azides (*general procedure*). Bis(oxazoline) **L1a** or **L1b**, 0.5 mmol, was dissolved in 2.5 mL of THF, and 21 mg (0.05 mmol, 10 mol %) of TTTA, a solution of 40 mg (0.2 mmol, 40 mol %) of sodium ascorbate in 0.25 mL of water, a solution of 10 mg (0.05 mmol) of copper(II) acetate monohydrate in 0.25 mL of water, and 67 mg (0.5 mmol) of benzyl azide were added under argon. The mixture was stirred for 20 h at room temperature until the reaction was complete (TLC; petroleum ether–EtOAc, 3:2), and 20 mL of methylene chloride and 20 mL of aqueous ammonium chloride were added. The organic phase was separated, the aqueous phase was extracted with methylene chloride (3× 10 mL), and the extracts were combined with the organic phase, dried over Na_2SO_4, and evaporated. The product was isolated by column chromatography (gradient elution with CH_2Cl_2–MeOH, 50:1 to 20:1).

(4*S*,4′*S*)-2,2′-[1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-propane-2,2-diyl]bis(4-phenyl-4,5-dihydro-1,3-oxazole) (L2a). Yield 208 mg (85%), yellow oily material. ^{1}H NMR spectrum, δ, ppm: 1.66 s (3H, CCH_3), 3.57–3.45 m (2H, CCH_2), 4.15–4.10 m (2H, CH_2O), 4.67–4.57 m (2H, CH_2O), 5.11–5.20 t (1H, NCH, ^3J = 8.4 Hz), 5.46–5.36 m (2H, C**H**$_2$Ph), 7.32–7.15 m (16H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.84 (C**C**H_3), 30.91 [**C**H$(CH_3)_2$], 33.16 [C(CH_3)**C**H_2], 53.74 (**C**H_2Ph), 53.99 (**C**CH_3), 55.99 and 56.09 (CH_2O), 123.13 (N**C**H=C); 126.47, 126.58, 127.59, 127.72, 127.75, 128.32, 128.40, 128.43, 128.73 (CH_{arom}); 134.49, 139.45, 142.96 (C_{arom}); 145.96 (NCH=**C**), 172.46 and 172.87 (NCO). Found: *m*/*z* 514.2234 $[M + Na]^+$. $C_{30}H_{29}N_5O_2$. Calculated: *M* + Na 514.2219.

(4*S*,4′*S*)-2,2′-[4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-propan-2,2-diyl]bis(4-isopropyl-4,5-dihydro-1,3-oxazole) (L2b). Yield 452 mg (87%), yellow oily material. ^{1}H NMR spectrum, δ, ppm: 0.77, 0.78 d [6H, CH(C**H**$_3)_2$, ^3J = 6.8 Hz], 0.84 d [6H, CH(C**H**$_3)_2$, ^3J = 6.8 Hz], 1.46 s (3H, CCH_3), 1.59–1.70 m [2H, C**H**$(CH_3)_2$], 3.28–3.43 m (2H, CCH_2), 3.78–3.93 m (4H, CH_2O, NCH), 4.08–4.10 d (1H, CH_2O, *J* = 8.4 Hz), 4.15–4.17 d (1H, CH_2O, *J* = 7.1 Hz), 5.40–5.50 m (2H, C**H**$_2$Ph), 7.17–7.38 m (6H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 17.61 and 17.79 [CH(**C**$H_3)_2$], 18.54 and 18.83 [CH(**C**$H_3)_2$], 22.86 (C**C**H_3), 28.83 [**C**H$(CH_3)_2$], 33.16 [C(CH_3)**C**H_2], 53.93 (**C**CH_3), 54.04 (**C**H_2Ph), 57.28 and 57.49 (CH_2O), 62.66 and 63.33 (NCH), 123.56 (N**C**H=C), 127.92 (2C, CH_{arom}), 128.59 (CH_{arom}), 128.96 (2C, CH_{arom}), 134.44 (C_{arom}), 143.74 (NCH=**C**), 172.95 and 173.62 (NCO). Found: *m*/*z* 446.5548 $[M + Na]^+$. $C_{24}H_{33}N_5O_2$. Calculated: *M* + Na 446.5508.

4-[(4*S*,4′*S*)-2,2′-Bis(4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl)propyl]-1*H*-1,2,3-triazol-1-ylmethyl polystyrene (L3). A 100-mL flask was charged with

1.12 g (3.84 mmol) of (4*S*,4′*S*)-2,2′-(pent-4-yn-2,2-diyl)bis(4-isopropyl-4,5-dihydro-1,3-oxazole), 2 g of azido polystyrene (*f* = 1.62 mmol/g), 20 mL of DMF–THF (1:1), 61 mg (0.32 mmol) of copper(I) iodide, 137 mg (0.32 mmol) of TTTA, and 0.827 g (1.11 mL, 6.4 mmol) of *N*,*N*-diisopropylethylamine (DIPEA). The mixture was stirred for 30 h at 60°C and filtered, and the precipitate was washed with DMF (400 mL), DMF–THF (1:1, 400 mL), and THF (400 mL) and dried under reduced pressure. Yield 2.82 g (96%), yellow powder, *f* = 1.06 mmol/g. IR spectrum (KBr), ν: 1657 cm^{-1} (C=N); no band assignable to azido group was observed. Found, %: C 80.35; H 7.91; N 7.45. $C_{62}H_{75}N_5O_2$. Calculated, %: C 80.78; H 8.14; N 7.60.

Copper(II) trifluoromethanesulfonate complex with 4-[(4*S*,4′*S*)-2,2′-bis(4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl)propyl]-1*H*-1,2,3-triazol-1-ylmethyl polystyrene [$Cu(OTf)_2$·L3]. A 100-mL flask was charged with 1.79 g of **L3** (*f* = 1.06 mmol/g), 50 mL of THF–DMF (1:1), and 687.3 mg (1.90 mmol) of $Cu(OTf)_2$. The mixture was stirred for 24 h, and the resulting resin was filtered off, washed with THF–DMF (1:1, 2×100 mL) and THF (2×100 mL), and dried under reduced pressure at 70°C. Yield 2.32 g (94%), green powder, *f* = 0.52 mmol/g. Found, %: C 69.07; H 6.84; N 6.30; S 5.54. $C_{62}H_{75}N_5O_2$·$Cu(OTf)_2$. Calculated, %: C 69.44; H 6.78; N 6.33; S 5.69.

Reaction of indoles with benzylidenemalonates (*general procedure*). A solution of 1 mmol of benzylidenemalonate **2a**–**2d** and 2 mmol of indole **1a**–**1f** in 4 mL of THF–EtOH (1:1) was cooled to –30°C, 200 mg (10 mol %) of $Cu(OTf)_2$·**L3** was added, and the mixture was stirred for 21 days at –30°C. When the reaction was complete (TLC, CH_2Cl_2–petroleum ether, 1:1), the catalyst was filtered off and washed with THF (5×10 mL) and methylene chloride (2×10 mL). The filtrate was evaporated, and the product was isolated by column chromatography using methylene chloride–petroleum ether (1:3 to 1:1) and then pure methylene chloride as eluents.

Diethyl (*S*)-2-[(1*H*-indol-3-yl)(phenyl)methyl]-malonate (3a). Yield 294 mg (81%), white powder, mp 178–179°C; published data [50]: mp 178–180°C; $[\alpha]_D^{20}$ = +73.0° (*c* = 1.00, CH_2Cl_2), 92.4% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 9.2 min (major isomer), 7.7 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those reported in [35].

Dimethyl (*S*)-2-[(1*H*-indol-3-yl)(phenyl)methyl]-malonate (3b). Yield 197 mg (58%), white powder, mp 147–149°C; published data [57]: mp 150–151°C; $[\alpha]_D^{20}$ = +27.9° (*c* = 1.00, CH_2Cl_2), 37.9% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 13.5 min (major isomer), 11.0 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those reported in [43].

Diethyl (*S*)-2-[(5-methoxy-1*H*-indol-3-yl)-(phenyl)methyl]malonate (3c). Yield 289 mg (73%), white powder, mp 118–120°C; published data [58]: mp 143–145°C, $[\alpha]_D^{20}$ = +14.0° (*c* = 1.00, CH_2Cl_2), 94.2% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 11.9 min (major isomer), 9.5 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those reported in [43].

Diethyl (*S*)-2-[(5-methyl-1*H*-indol-3-yl)(phenyl)-methyl]malonate (3d). Yield 346 mg (91%), white powder, mp 174.5–176°C; published data [58]: mp 176.5–178°C, $[\alpha]_D^{20}$ = +39.5° (*c* = 1.00, CH_2Cl_2), 91.2% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 6.9 min (major isomer), 8.3 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those reported in [43].

Diethyl (*S*)-2-[(5-bromo-1*H*-indol-3-yl)(phenyl)-methyl]malonate (3e). Yield 374 mg (84%), white powder, mp 146–147°C, $[\alpha]_D^{20}$ = –12.9° (*c* = 1.00, CH_2Cl_2), 87.2% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 8.9 min (major isomer), 7.3 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those reported in [59].

Diethyl (*S*)-2-[(1-methyl-1*H*-indol-3-yl)(phenyl)-methyl]malonate (3f). Yield 195 mg (51%), white powder, mp 84.5–85.5°C; published data [60]: mp 87–88°C; $[\alpha]_D^{20}$ = +50.4° (*c* = 1.00, CH_2Cl_2), 66.2% *ee* [Daicel Chiralcel AD-H; hexane–propan-2-ol, 90:10, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 20.9 min (major isomer), 26.0 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those reported in [46].

Diethyl (*S*)-2-[(4-bromophenyl)(1*H*-indol-3-yl)-methyl]malonate (3g). Yield 355 mg (80%), white powder, mp 146–147°C; published data [61]: mp 148–150°C; $[\alpha]_D^{20}$ = +25.5° (*c* = 1.00, CH_2Cl_2), 88.8% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 8.7 min (major isomer), 8.1 min (minor isomer)]. The

^{1}H and ^{13}C NMR spectra were consistent with those reported in [35].

Diethyl (*S*)-2-[(4-bromophenyl)(5-methoxy-1*H*-indol-3-yl)methyl]malonate (3h). Yield 409 mg (86%), white powder, mp 141–142°C, $[\alpha]_D^{20}$ = –23.5° (*c* = 1.00, CH_2Cl_2), 89.4% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 90:10, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 15.7 min (major isomer), 14.8 min (minor isomer)]. ^{1}H NMR spectrum, δ, ppm: 1.01 t and 1.06 t (3H, OCH_2CH_3, ^3J = 7.1 Hz), 3.78 s (3H, OCH_3), 4.01 t and 4.02 t (OCH_2CH_3, ^3J = 7.1 Hz), 4.21 d.d [1H, C**H**$(COOEt)_2$, ^3J = 11.6, ^4J = 1.4 Hz], 4.99 d (1H, 3-CH, ^3J = 11.6 Hz), 6.80 d.d (1H, H_{arom}, ^3J = 8.8, ^4J = 2.4 Hz), 6.90 d (1H, H_{arom}, *J* = 2.3 Hz), 7.10–7.15 m (1H, H_{arom}), 7.15–7.21 m (1H, H_{arom}), 7.21–7.26 m (2H, H_{arom}), 7.33–7.39 m (2H, H_{arom}), 7.98 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.90 and 13.96 (OCH_2CH_3), 42.34 (3-CH), 55.96 (OCH_3), 58.20 [**C**H$(COOEt)_2$], 61.72 (OCH_2CH_3), 101.22 (CH_{arom}), 111.90 (CH_{arom}), 112.67 (CH_{arom}), 116.25 (C_{arom}), 120.73 (C_{arom}), 121.73 (CH_{arom}), 127.07 (C_{arom}), 129.58 (C_{arom}), 130.08 (2C, CH_{arom}), 131.57 (2C, CH_{arom}), 140.64 (C_{arom}), 154.15 (C^5), 167.66 and 167.93 (C=O). Found: *m*/*z* 473.0760 $[M]^+$. $C_{23}H_{24}BrNO_5$. Calculated: *M* 473.0838.

Diethyl (*S*)-2-[(4-bromophenyl)(5-methyl-1*H*-indol-3-yl)methyl]malonate (3i). Yield 375 mg (82%), white powder, mp 170–171°C, $[\alpha]_D^{20}$ = –2.2° (*c* = 1.00, CH_2Cl_2), 90.9% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 8.2 min (major isomer), 7.3 min (minor isomer)]. ^{1}H NMR spectrum, δ, ppm: 1.00 t and 1.06 t (3H, OCH_2CH_3, ^3J = 7.1 Hz), 2.39 s (3H, 5-CH_3), 3.98–4.04 m (4H, OCH_2CH_3), 4.23 d [1H, C**H**$(COOEt)_2$, ^3J = 11.7 Hz], 5.02 d (1H, 3-CH, ^3J = 11.6 Hz), 6.97 d (1H, H_{arom}, ^3J = 8.3 Hz), 7.08–7.15 m (1H, H_{arom}), 7.18 d (1H, H_{arom}, ^3J = 8.3 Hz), 7.22–7.31 m (3H, H_{arom}), 7.32–7.41 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.87 and 13.96 (OCH_2CH_3), 21.65 (5-CH_3), 42.32 (3-CH), 58.31 [**C**H$(COOEt)_2$], 61.68 (OCH_2CH_3), 110.87 (CH_{arom}), 116.03 (C_{arom}), 118.87 (CH_{arom}), 120.68 (C_{arom}), 121.11 (CH_{arom}), 124.22 (CH_{arom}), 126.86 (CH_{arom}), 129.01 (C_{arom}), 130.10 (2C, CH_{arom}), 131.55 (2C, CH_{arom}), 134.68 (C_{arom}), 140.80 (C_{arom}), 167.83 and 167.89 (C=O). Found: *m*/*z* 457.0750 $[M]^+$. $C_{23}H_{24}BrNO_5$. Calculated: *M* 457.0888.

Diethyl (*S*)-2-[(5-bromo-1*H*-indol-3-yl)(4-bromophenyl)methyl]malonate (3j). Yield 408 mg (78%), white powder, mp 157–158°C, $[\alpha]_D^{20}$ = –53.2° (*c* = 1.00, CH_2Cl_2), 85.7% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 8.5 min (major isomer), 7.8 min (minor isomer)]. ^{1}H NMR spectrum, δ, ppm: 1.01 t and 1.07 t (3H, CH_3, ^3J = 7.2 Hz), 3.93–4.10 m (4H, OCH_2), 4.20 d [1H, C**H**$(COOEt)_2$, ^3J = 11.6 Hz], 4.97 d (1H, 3-CH, ^3J = 11.6 Hz), 7.21–7.24 m (3H, H_{arom}), 7.15–7.18 m (2H, H_{arom}), 7.30–7.43 m (2H, H_{arom}), 7.63 d (1H, H_{arom}, ^4J = 1.8 Hz), 8.14 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.89 and 13.97 (OCH_2CH_3), 43.06 (3-CH), 58.23 [**C**H$(COOEt)_2$], 61.81 (OCH_2CH_3), 112.74 (CH_{arom}), 113.19 (C_{arom}), 116.26 (C_{arom}), 120.97 (C_{arom}), 121.82 (CH_{arom}), 122.38 (CH_{arom}), 125.55 (CH_{arom}), 128.33 (C_{arom}), 129.95 (2C, CH_{arom}), 131.73 (2C, CH_{arom}), 134.91 (C_{arom}), 140.25 (C_{arom}), 167.59 and 167.76 (C=O). Found: *m*/*z* 543.9687 $[M + Na]^+$. $C_{22}H_{21}Br_2NO_4$. Calculated: *M* + Na 543.9735.

Diethyl (*S*)-2-[(4-bromophenyl)(1-methyl-1*H*-indol-3-yl)methyl]malonate (3k). Yield 210 mg (46%), white powder, mp 116–117°C, $[\alpha]_D^{20}$ = +13.7° (*c* = 1.00, CH_2Cl_2), 85.7% *ee* [Daicel Chiralcel AD-H; hexane–propan-2-ol, 90:10, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 26.9 min (major isomer), 35.7 min (minor isomer)]. ^{1}H NMR spectrum, δ, ppm: 1.00 t and 1.06 t (3H, OCH_2CH_3, ^3J = 7.1 Hz), 3.74 s (3H, NCH_3), 3.92–4.06 m (4H, OCH_2CH_3), 4.22 d [1H, C**H**$(COOEt)_2$, ^3J = 11.6 Hz], 5.03 d (1H, 3-CH, ^3J = 11.6 Hz), 6.96–7.08 m (2H, H_{arom}), 7.10–7.28 m (4H, H_{arom}), 7.29–7.40 m (2H, H_{arom}), 7.49 d (1H, H_{arom}, *J* = 7.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.86 and 13.95 (OCH_2CH_3), 32.92 (NCH_3), 42.33 (3-CH), 58.23 [**C**H$(COOEt)_2$], 61.64 (OCH_2CH_3), 109.29 (CH_{arom}), 114.93 (C_{arom}), 119.26 (CH_{arom}), 119.42 (CH_{arom}), 120.62 (C_{arom}), 122.07 (CH_{arom}), 125.81 (CH_{arom}), 127.05 (C_{arom}), 130.04 (2C, CH_{arom}), 131.54 (2C, CH_{arom}), 137.13 (C_{arom}), 140.97 (C_{arom}), 167.77 and 167.87 (C=O). Found: *m*/*z* 457.0940 $[M]^+$. $C_{23}H_{24}BrNO_4$. Calculated: *M* 457.0888.

Diethyl (*S*)-2-[(4-bromophenyl)(5-iodo-1*H*-indol-3-yl)methyl]malonate (3l). Yield 433 mg (76%), white powder, mp 183–184°C, $[\alpha]_D^{20}$ = –67.2° (*c* = 1.00, CH_2Cl_2), 86.4% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 8.5 min (major isomer), 7.7 min (minor isomer)]. ^{1}H NMR spectrum, δ, ppm: 1.01 t and 1.07 t (3H, OCH_2CH_3, ^3J = 7.1 Hz), 3.94–4.08 m (4H, OCH_2CH_3), 4.19 d [1H, C**H**$(COOEt)_2$, ^3J = 11.6 Hz], 4.97 d (1H, 3-CH, ^3J = 11.6 Hz), 7.05–7.15 m (2H, H_{arom}), 7.17–7.25 m (2H, H_{arom}), 7.33–

7.45 m (3H, H_{arom}), 7.84 s (1H, CH_{arom}), 8.12 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.92 and 13.98 ($OCH_2\mathbf{C}H_3$), 42.00 (3-CH), 58.30 [$\mathbf{C}H(COOEt)_2$], 61.81 ($O\mathbf{C}H_2CH_3$), 83.42 (C^5), 113.23 (CH_{arom}), 116.01 (C_{arom}), 120.97 (C_{arom}), 121.99 (CH_{arom}), 128.10 (CH_{arom}), 129.16 (C_{arom}), 129.95 (2C, CH_{arom}), 131.03 (CH_{arom}), 131.74 (2C, CH_{arom}), 135.34 (C_{arom}), 140.28 (C_{arom}), 167.59 and 167.74 (C=O). Found: m/z 568.9640 $[M]^+$. $C_{22}H_{21}BrINO_4$. Calculated: M 568.9698.

Diethyl (*S*)-2-[(1*H*-indol-3-yl)(4-nitrophenyl)-methyl]malonate (3m). Yield 410 mg (99%), yellow powder, mp 108–110°C; published data [61]: mp 105–107°C; $[\alpha]_D^{20}$ = +9.1° (c = 1.00, CH_2Cl_2), 85.5% *ee* [Daicel Chiralcel AS-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 21.1 min (major isomer), 34.5 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those given in [43].

Diethyl (*S*)-2-[(5-methoxy-1*H*-indol-3-yl)-(4-nitrophenyl)methyl]malonate (3n). Yield 305 mg (69%), yellow powder, mp 157–158°C, $[\alpha]_D^{20}$ = –49.8° (c = 1.00, CH_2Cl_2), 78.0% *ee* [Daicel Chiralcel AS-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 27.0 min (major isomer), 33.8 min (minor isomer)]. ^1H NMR spectrum, δ, ppm: 1.02 t and 1.07 t (3H, $OCH_2C\mathbf{H}_3$, ^3J = 7.1 Hz), 3.79 s (3H, OCH_3), 3.98–4.08 m (4H, $OC\mathbf{H}_2CH_3$), 4.28 d [1H, C**H**$(COOEt)_2$, ^3J = 11.5 Hz], 5.14 d (1H, 3-CH, ^3J = 11.5 Hz), 6.82 d.d (1H, H_{arom}, ^3J = 8.8, ^4J = 2.3 Hz), 6.89 d (1H, H_{arom}, ^4J = 2.2 Hz), 7.16–7.23 m (2H, H_{arom}), 7.54 d (2H, H_{arom}, ^3J = 8.7 Hz), 8.03 s (1H, NH), 8.11 d (2H, H_{arom}, ^3J = 8.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.90 and 14.01 ($OCH_2\mathbf{C}H_3$), 42.52 (3-CH), 56.00 (5-OCH_3), 57.80 [$\mathbf{C}H(COOEt)_2$], 61.93 ($O\mathbf{C}H_2CH_3$), 100.99 (CH_{arom}), 112.08 (CH_{arom}), 112.85 (CH_{arom}), 115.26 (C_{arom}), 122.03 (CH_{arom}), 123.80 (2C, CH_{arom}), 126.89 (C_{arom}), 129.23 (2C, CH_{arom}), 131.46 (C_{arom}), 149.33 (C_{arom}), 154.35 (C^5), 167.56 (C=O). Found: m/z 463.1463 $[M + Na]^+$. $C_{23}H_{24}N_2O_7$. Calculated: M + Na 463.1481.

Diethyl (*S*)-2-[(5-iodo-1*H*-indol-3-yl)(4-nitrophenyl)methyl]malonate (3o). Yield 436 mg (81%), white powder, mp 181–182°C, $[\alpha]_D^{20}$ = –98.6° (c = 1.00, CH_2Cl_2), 78.0% *ee* [Daicel Chiralcel AS-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 21.5 min (major isomer), 28.9 min (minor isomer)]. ^1H NMR spectrum, δ, ppm: 1.03 t and 1.07 t (3H, $OCH_2C\mathbf{H}_3$, ^3J = 7.1 Hz), 3.96–4.09 m (4H, $OC\mathbf{H}_2CH_3$), 4.27 d [1H, C**H**$(COOEt)_2$, ^3J = 11.5 Hz], 5.12 d (1H, 3-CH, ^3J = 11.5 Hz), 7.10 d (1H, H_{arom}, ^3J = 8.5 Hz), 7.17 d (1H, H_{arom}, ^4J = 2.2 Hz), 7.41 q (2H, H_{arom}, J = 8.6, 1.1 Hz), 7.52 d (2H, H_{arom}, ^3J = 8.6 Hz), 7.83 s (1H, H_{arom}), 8.12 d (1H, H_{arom}, ^3J = 8.7 Hz), 8.23 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.91 and 14.01 ($OCH_2\mathbf{C}H_3$), 42.18 (3-CH), 57.88 [$\mathbf{C}H(COOEt)_2$], 62.02 ($O\mathbf{C}H_2CH_3$), 83.62 (C^5), 113.40 (CH_{arom}), 114.92 (C_{arom}), 122.32 (CH_{arom}), 123.94 (2C, CH_{arom}), 127.80 (CH_{arom}), 128.93 (C_{arom}), 129.14 (2C, CH_{arom}), 131.26 (CH_{arom}), 135.33 (C_{arom}), 146.99 (C_{arom}), 148.88 (C_{arom}), 167.33 and 167.40 (C=O). Found: m/z 559.0320 $[M + Na]^+$. $C_{22}H_{21}IN_2O_6$. Calculated: M + Na 559.0342.

Addition of indoles to (*E*)-2-oxo-4-phenylbut-3-enoate (*general procedure*). A solution of 380 mg (2 mmol) of (*E*)-2-oxo-4-phenylbut-3-enoate (**4**) and 1 mmol of indole **1a**–**1f** in 4 mL of THF–MeOH (1:1) was cooled to –30°C, 200 mg (10 mol %) of $Cu(OTf)_2 \cdot$ **L3** was added, and the mixture was kept for 27 days at –30°C. When the reaction was complete (TLC, Et_2O–petroleum ether, 1:1), the catalyst was filtered off and washed with THF (5×10 mL) and methylene chloride (2×10 mL). The filtrate was evaporated, and the product was isolated by column chromatography (gradient elution with Et_2O–petroleum ether, 1:3 to 1:1).

Methyl (*S*)-4-(1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (5a). Yield 253 mg (82%), white powder, mp 137–138°C; published data [62]: mp 99–102°C, $[\alpha]_D^{20}$ = –22.7° (c = 1.00, CH_2Cl_2), –12.0 (c = 1.00, $CHCl_3$), 30.9% *ee* [Daicel Chiralcel D-H; hexane–propan-2-ol, 80:20, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 18.4 min (major isomer), 16.8 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those given in [36].

Methyl (*S*)-4-(5-methoxy-1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (5b). Yield 229 mg (68%), orange powder, mp 134–136°C; published data [63]: mp 135–136°C, $[\alpha]_D^{20}$ = +10.1° (c = 1, CH_2Cl_2), 32.6% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 80:20, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 19.5 min (major isomer), 21.4 min (minor isomer)]. The ^1H and ^{13}C NMR spectra were consistent with those given in [36].

Methyl (*S*)-4-(5-methyl-1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (5c). Yield 233 mg (73%), orange powder, mp 137–139°C; published data [62]: mp 125–126°C; $[\alpha]_D^{20}$ = +6.8° (c = 0.99, CH_2Cl_2), 36.6% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 85:15, flow rate 1 mL/min; 25°C, λ 254 nm; retention time

20.3 min (major isomer), 21.3 min (minor isomer)]. The ^{1}H and ^{13}C NMR spectra were consistent with those given in [51].

Methyl (*S*)-4-(5-bromo-1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (5d). Yield 304 mg (79%), orange powder, mp 160–161°C, $[\alpha]_D^{20}$ = +9.9° (*c* = 0.51, CH_2Cl_2), 53.8% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 90 : 10, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 46.5 min (major isomer), 50.6 min (minor isomer)]. The ^{1}H and ^{13}C NMR spectra were consistent with those given in [54].

Methyl (*S*)-4-(5-iodo-1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (5e). Yield 272 mg (66%), white powder, mp 152.5–153.5°C, $[\alpha]_D^{20}$ = +16.0° (*c* = 1.02, CH_2Cl_2), 83.1% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 80 : 20, flow rate 0.5 mL/min; 25°C, λ 254 nm; retention time 46.0 min (major isomer), 49.9 min (minor isomer)]. ^{1}H NMR spectrum, δ, ppm: 3.58 d.d (1H, CH_2CO, ^2J = 17.6, ^3J = 7.6 Hz), 3.62 d.d (1H, CH_2CO, ^2J = 17.0, ^3J = 7.2 Hz), 3.76 s (3H, OCH_3), 4.85 t (1H, 3-CH, ^3J = 7.6 Hz), 6.99 d (1H, 2-H, ^3J = 2.4 Hz), 7.09 d (1H, H_{arom}, ^3J = 8.8 Hz), 7.18–7.22 m (1H, H_{arom}), 7.28–7.32 m (4H, H_{arom}), 7.36 d.d (1H, H_{arom}, ^3J = 8.8, ^4J = 1.8 Hz), 7.70–7.74 m (1H, H_{arom}), 8.07 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 37.40 (3-CH), 45.64 (**C**H_2CO), 53.00 (OCH_3), 83.07 (C^5), 113.11 (CH_{arom}), 117.71 (C_{arom}), 122.27 (CH_{arom}), 127.60 (CH_{arom}), 126.78 (CH_{arom}), 128.12 (2C, CH_{arom}), 128.64 (2C, CH_{arom}), 128.95 (C_{arom}), 130.68 (CH_{arom}), 135.53 (C_{arom}), 142.66 (C_{arom}), 161.18 (**C**$OOCH_3$), 192.33 (CH_2**C**O). Found, *m*/*z*: 456.0051 $[M + Na]^+$, 432.0086 $[M]^-$. $C_{19}H_{16}INO_3$. Calculated: *M* + Na 456.0073, *M* 432.0102.

Methyl (*S*)-4-(1-methyl-1*H*-indol-3-yl)-2-oxo-4-phenylbutanoate (5f). Yield 213 mg (66%), orange powder, mp 118–119°C; published data [36]: mp 100°C, $[\alpha]_D^{20}$ = –14.1° (*c* = 0.64, $CHCl_3$), 5.9% *ee* [Daicel Chiralcel OD-H; hexane–propan-2-ol, 80 : 20, flow rate 1 mL/min; 25°C, λ 254 nm; retention time 18.9 min (major isomer), 16.1 min (minor isomer)]. The ^{1}H and ^{13}C NMR spectra were consistent with those given in [36].

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