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# Enantioselective Copper(II)/Box-catalyzed Synthesis of Chiral $\beta^3$-tryptophan derivatives

Elena A. Tarasenko, Ivan V. Shestakov, Victor B. Rybakov, and Irina P. Beletskaya*[a]

*β*-Amino acids and their derivatives are important building blocks for the preparation of various bioactive compounds and materials. We developed a highly efficient method for the synthesis of $\beta^3$-tryptophan derivatives based on enantioselective Friedel-Crafts alkylation of indoles with phthaloyl-protected aminomethylenemalonate in the presence of chiral $Cu(OTf)_2$/*i*PrBox complex as a catalyst. A wide range of indoles with electron-donating and electron-withdrawing substituents gave the desired products in high yields (up to 99%) and excellent enantioselectivities (up to 99% *ee*). In the case of pyrrole the Friedel-Crafts product was obtained in up to 90% yield and up to 82% *ee*.

## Introduction

*β*-Amino acid moiety is an important structural unit of many bioactive natural compounds[1] used as effective drugs, e.g., paclitaxel[2] (antitumor), ubenimex[3] (immunosuppressant, antitumor), bleomycin[4] (antibiotic, antitumor), penicillins[5a-d] and cephalosporins[5b-f] (antibiotics). In recent years enantiopure *β*-amino acids and their derivatives have attracted attention due to their application in the synthesis of new biologically active compounds[6] and materials[7] on the base of α,*β*- and *β*-peptides. The incorporation of *β*-amino acid residues into peptides and proteins renders new important properties such as improved bioactivity, enhanced resistance to enzymatic degradations, propensity to fold and form well-defined secondary structures (helices, sheets, turns). In this aspect *β*-peptide oligomers (foldamers[8]) are considered as promising protease-resistant peptidomimetics.[9] Moreover, β-peptide secondary structural units are capable of self-assembly that leads to forming nanostructured materials with varied morphologies: fibrils, vesicles, liquid crystals, hydrogels, microtubes, etc.[7]
There are many ways to synthesize different types of *β*-amino acids (Figure 1). Particularly important is the asymmetric synthesis leading to enantiopure *β*-amino acids.[10] Among the latter, special place is occupied by *β*-amino acids bearing indole moiety as a privileged group for organic synthesis of bioactive compounds. The asymmetric Friedel-Crafts reaction of indoles with various electrophiles is one of the most straightforward methods to afford chiral indole derivatives.[11] Using this method $\beta^2$- and $\beta^{2,2}$-tryptophan derivatives were obtained by the reaction of indoles and Michael acceptors such as *β*-nitroacrylates and α-substituted *β*-nitroacrylates. For asymmetric induction chiral *β*-nitroacrylate was used in the case of $\beta^2$-derivatives,[12] whereas either Ni (II) chiral complex[13] or chiral phosphoric acid[14] were employed as a catalyst to prepare optically active $\beta^{2,2}$-derivatives.

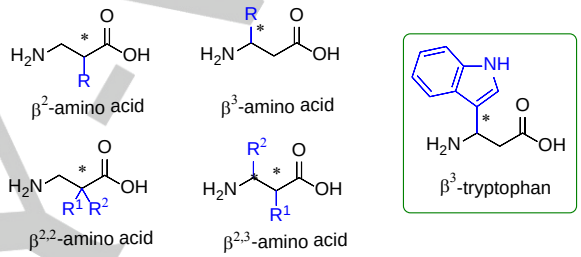
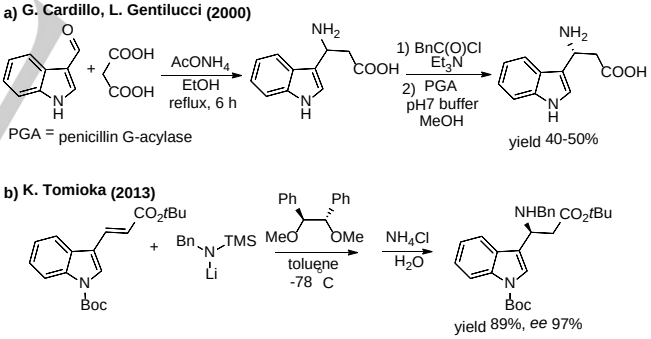



**Figure 1.** The most common types of *β*-amino acids and $\beta^3$-tryptophan.




**Scheme 1.** Literature examples of the synthesis of $\beta^3$-tryptophan (a) and its derivative (b).

According to our knowledge, the general method of the preparation of $\beta^3$-tryptophans (Figure 1) has not been reported. Until now there are only two examples of the synthesis of unsubstituted $\beta^3$-tryptophan[15] (Scheme 1a) and its derivative[16] (Scheme 1b). It is known that indoles can be alkylated with the benzylidene malonates.[17] To our surprise, we could not find any mention of such Friedel-Crafts alkylation for the synthesis of $\beta^3$-tryptophan derivatives. One may assume that the application of *N*-protected aminomethylenemalonates as the alkylating agents could hamper the reaction. However, we have shown that the reaction proceeds successfully to give good yields and excellent

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enantioselectivity under mild conditions with properly chosen protective group, Lewis acid, ligand and solvent.

Herein, we present the first enantioselective Friedel–Crafts reaction of indoles with protected aminomethylenemalonates as a highly efficient method for the preparation of the $\beta^3$-tryptophan derivatives.

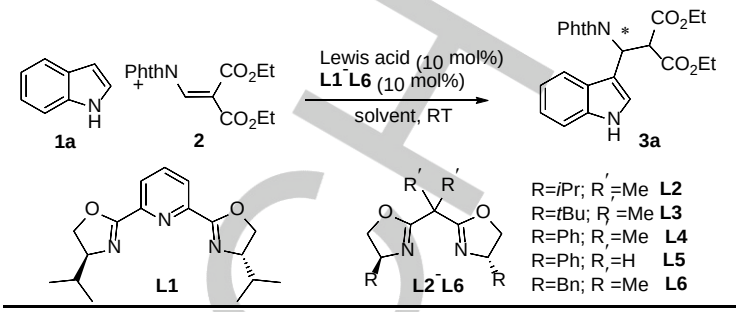
## Results and Discussion

Initially, aminomethylenemalonate with phthlaloyl protective group was chosen as Michael acceptor. Phthalimide group has planar structure, and, according to our assumption, phthalimidomethylenemalonate could react with indole similar to benzylidenemalonates.[17] In addition, the phthalimide group itself can impart a certain biological activity to the amino acid derivatives. For example, phthaloyl-protected L-tryptophan (RG108) is an inhibitor of DNA-methyltransferase of the DNMT1 family.[18]

At first we investigated the non-asymmetric reaction of indole (**1a**) with phthalimidomethylenemalonate **2** using Yb(III), Sc(III), Cu(II), Mg(II), Zn(II), Ni(II), In(III) salts as catalysts in $CH_2Cl_2$ at room temperature (See Supporting Information, Table S1). This screening revealed that $Yb(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$ are by far the best Lewis acids for this reaction. Then the enantioselective reaction with chiral complexes of $Yb(OTf)_3$ and $Sc(OTf)_3$ with (*S*,*S*)-*i*PrPyBox (**L1)** ligand (Table 1, entries 1 and 2) and $Cu(OTf)_2$ with (*S*,*S*)-*i*PrBox ligand (**L2)** (Table 1, entries 3–13) was studied in different solvents. Surprisingly, $Yb(OTf)_3$/**L1** or $Sc(OTf)_3$/**L1** complexes did not promote this reaction in either $CH_2Cl_2$ or $Et_2O$ (entries 1 and 2). To our delight, the reaction in the presence of 10 mol% of $Cu(OTf)_2$/**L2** proceeded smoothly at room temperature, and the best result was achieved in 1,4-dioxane (entry 10). The product **3a** was obtained in high isolated yield (95%) and high enantioselectivity (95%) after 24 h. The addition of molecular sieves 4Å resulted in an increase of yield up to 99%, but the enantiomeric excess (93%) slightly decreased (entry 11). The reactions in $CH_2Cl_2$ (entry 3) and $CHCl_3$ (entry 4) gave the product also in high yields (89% and 92%), but enantiomeric excesses were even lower (88% and 75% *ee*). In the cases of trifluoromethylbenzene (entry 5) and toluene (entry 6) both lower yields (73% and 86%) and lower enantioselectivity (57% and 67% *ee*) were observed. The use of oxygen-containing aprotic solvents (entries 8–12) except diethyl ether (entry 7) led to the product in good to excellent yields (82–95%) and high enantioselectivity (90–96% *ee*). Ethanol and propan-2-ol are not useful as solvents, because the Michael addition of these alcohols to the alkene **2** is observed. The non-nucleophilic *tert*-butanol did not react with **2**, but in this solvent the yield of Friedel-Crafts product **3a** (74%) and enantiomeric excess (83% *ee*) were not as high (entry 13).

The effect of counter-ion type and structure of Box ligand on the reaction outcome was investigated in the next series of experiments. The use of $Cu(SbF_6)_2$/**L2** complex with weakly coordinating counter-ion led to decrease in the yield (85%) and *ee* (92%) (entry 14). Ligands **L3**–**L5** were less effective than **L2**. With *t*BuBox (**L3**) the product was obtained in lower yield (39%) but good enantioselectivity (90%) (entry 15), while with two types of PhBox (**L4** and **L5**) the product was obtained with lower enantioselectivity (34% and 51% *ee*) but in good yields (90%

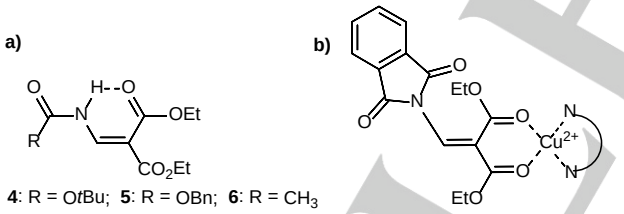
**Table 1.** Optimization of the reaction conditions.




| Entry[a] | Lewis acid | Ligand | Solvent | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | $Yb(OTf)_3$ | **L1** | $CH_2Cl_2$ or $Et_2O$ | 24 | 0 | – |
| 2 | $Sc(OTf)_3$ | **L1** | $CH_2Cl_2$ or $Et_2O$ | 24 | 0 | – |
| 3 | $Cu(OTf)_2$ | **L2** | $CH_2Cl_2$ | 24 | 89 | 88 |
| 4 | $Cu(OTf)_2$ | **L2** | $CHCl_3$ | 24 | 92 | 75 |
| 5 | $Cu(OTf)_2$ | **L2** | $PhCF_3$ | 24 | 73 | 57 |
| 6 | $Cu(OTf)_2$ | **L2** | $PhCH_3$ | 24 | 86 | 67 |
| 7 | $Cu(OTf)_2$ | **L2** | $Et_2O$ | 24 | 88 | 70 |
| 8 | $Cu(OTf)_2$ | **L2** | THF | 24 | 82 | 96 |
| 9 | $Cu(OTf)_2$ | **L2** | DME | 24 | 85 | 93 |
| 10 | $Cu(OTf)_2$ | **L2** | 1,4-dioxane | 24 | 95 | 95 |
| 11 | $Cu(OTf)_2$ | **L2** | 1,4-dioxane + 4Å MS | 24 | 99 | 93 |
| 12 | $Cu(OTf)_2$ | **L2** | MTBE | 24 | 91 | 90 |
| 13 | $Cu(OTf)_2$ | **L2** | *t*BuOH | 24 | 74 | 83 |
| 14 | $Cu(SbF_6)_2$ | **L2** | 1,4-dioxane | 24 | 85 | 92 |
| 15 | $Cu(OTf)_2$ | **L3** | 1,4-dioxane | 24 | 39 | 90 |
| 16 | $Cu(OTf)_2$ | **L4** | 1,4-dioxane | 24 | 90 | 34 |
| 17 | $Cu(OTf)_2$ | **L5** | 1,4-dioxane | 24 | 84 | 51 |
| 18 | $Cu(OTf)_2$ | **L6** | 1,4-dioxane | 24 | 97 | 94 |
| **19**[d] | **$Cu(OTf)_2$** | **L2** | **1,4-dioxane/DME (10:1)** | **48** | **94** | **98** |
| 20[d] | $Cu(OTf)_2$ | **L6** | 1,4-dioxane/DME (10:1) | 48 | 94 | 97 |

[a] Reaction conditions: indole (**1a**) (0.275 mmol), phthalimidomethylenemalonate **2** (0.25 mmol), Lewis acid (10 mol%), ligand **L1**–**L6** (10 mol%), solvent (1.5 ml), room temperature. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at +5°C.

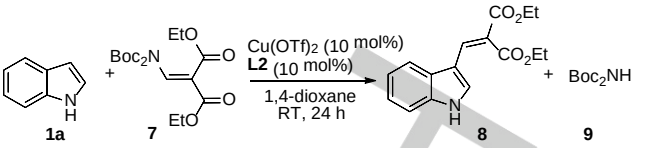
and 84%) (entries 16 and 17). BnBox ligand (**L6**) showed the same efficiency as *i*PrBox (**L2**), giving the product in high yield (97%) and high enantiomeric excess (94% *ee*) (entry 18).
Further, these two ligands (**L2** and **L6**) were used in the reaction at +5 °C to further enhance the enantioselectivity (entries 19 and 20). Although the reaction time then had to be increased to 48 h, excellent enantiomeric excesses (98% *ee* for **L2** and 97% for **L6**) and high yield in both cases (94%) were achieved. It should be noted that in all of the experiments (Table 1) the same enantiomer was predominantly formed according to the HPLC data.
Since the removal of phthaloyl group from product **3a** happened to be difficult,[19] we tried in the reaction with indole several aminomethylenemalonates with other protective groups but without success. The reaction did not proceed with BocNH- and CbzNH-substituted methylenemalonates **4** and **5** in the presence of 10 mol% $Cu(OTf)_2$/**L2** even at room temperature. For AcNH-substituted methylenemalonate **6** low conversion was observed and we obtained complex mixture of products. Low reactivity of the compounds **4**–**6** can be explained by the formation of an intramolecular hydrogen bond between NH-hydrogen and the carbonyl oxygen of the ester group (Figure 2a), which would prevent the complexation of Lewis acid with the substrate. This problem does not arise in the case of phthalimidomethylene-malonate **2** (Figure 2b). The formation of an intramolecular hydrogen bond in compounds **4**–**6** is confirmed by $^1$H NMR- and IR-spectroscopy. The signals of NH-protons appear in the low field region at 10.13, 10.35 and 10.85 ppm for **4**, **5** and **6** respectively. In the IR-spectra of these compounds, the absorption bands at 3270, 3298 and 3293 $cm^{-1}$ for **4**, **5** and **6** respectively, can be assigned to vibration modes of the hydrogen-bonded NH-groups.[20]



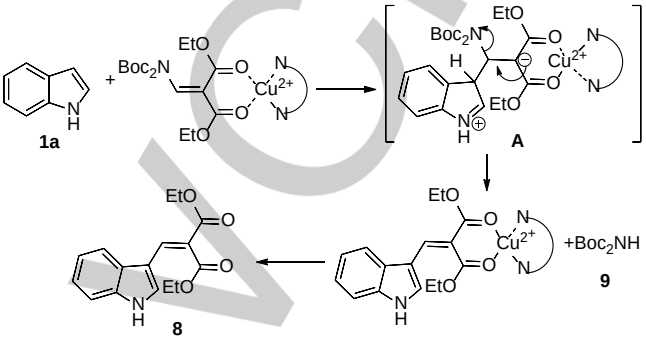

**4**: R = O*t*Bu; **5**: R = OBn; **6**: R = $CH_3$

**Figure 2.** Intramolecular hydrogen bond formation in compounds **4**–**6** (a); Lewis acid activation of compound **2** (b).

To avoid the formation of an intramolecular hydrogen bond in the substrate, $Boc_2N$-substituted alkene **7** was tested in the reaction with indole. However, in the place of expected product, $Boc_2N$ group was cleaved to give only 2-((1*H*-indol-3-yl)methylene)malonate (**8**) and $Boc_2NH$ (**9**) (Scheme 2) instead with isolated yields of 79% and 88%, respectively. The proposed reaction mechanism is presented in Scheme 3. Apparently, $Boc_2N$ makes a good leaving group in β-elimination from intermediate A, and such pathway, quite common in indole chemistry, is favored here by steric congestion in the intermediate, and the formation of the energetically favorable conjugated system **8**.




**Scheme 2.** Reaction of the indole (**1a**) and alkene **7**.




**Scheme 3.** A plausible mechanism of the formation of compounds **8** and **9**.

Since the use of other protective groups did not lead to the desired result, the studies were continued with phthalimidomethylenemalonate **2**. Under the optimized conditions established for indole (**1a**) (Table 2, entry 1), the scope of reaction was extended by using indoles with electron-donating and electron-withdrawing substituents in 1,2,4,5 and 6 positions. *N*-methyl substituted indole (**1b**) gave 83% and only 74% *ee* (Table 2, entry 2). This fact can indicate that the NH-proton of indole plays an essential role in providing high enantioselectivity. A decrease in the enantiomeric excess was also observed previously in the asymmetric reactions of *N*-methylindole with benzylidenemalonates.[17a, 21] Reaction with 2-phenylindole (**1c**) did not proceed even at room temperature probably due to steric effect (entry 3), but indole **1d** with smaller methyl group in position 2 reacted smoothly in high yield (99%) and good enantioselectivity (79% *ee*) (entry 3). All 4- and 5-substituted indoles independently of substituent (entries 5–8, 10–12) gave high yields (89–97%) and excellent enantioselectivity (96–99% *ee*). Only 5- and 6-chloroindoles (**1i**) and (**1m**) gave products in 78% and 83% yields but excellent *ee* (98%) (entries 9 and 13). The reaction with indoles **1n** and **1o** bearing strong withdrawing $CO_2Me$ group in position 5 and 6 proceeded slowly and the yields of products were only 54% and 37% after 72 h, but enantioselectivity was again excellent (98 and >99%, respectively) (entries 14 and 15).
To determine the absolute configuration of products **3**, prepared by reaction of indoles **1** with phthalimidomethylenemalonate **2**, a single crystal of compound **3k** with bromine as the heavy atom was obtained by recrystallization from hexane/dichloromethane. The absolute configuration of the chiral center in the product **3k** has been determined to be (*R*) by X-ray analysis (Figure 3).[22] The configurations of other products **3** were tentatively assigned

to be the same by the assumption of a uniform mechanistic pathway.

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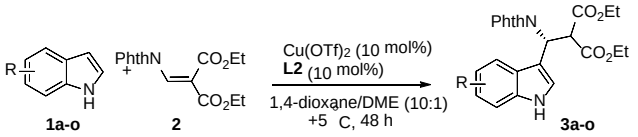
**Table 2.** Enantioselective Friedel-Crafts reaction of indoles **1a**–**o** with phthalimidomethylenemalonate **2**.




**1a-o** **2** **3a-o**

| Entry[a] | Indole | R | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **1a** | H | **3a** | 94 | 98 |
| 2 | **1b** | 1-Me | **3b** | 83 | 74 |
| 3[d] | **1c** | 2-Ph | **3c** | 0 | – |
| 4 | **1d** | 2-Me | **3d** | 99 | 79 |
| 5 | **1e** | 4-OMe | **3e** | 93 | 96 |
| 6 | **1f** | 5-OMe | **3f** | 93 | 98 |
| 7 | **1g** | 5-Me | **3g** | 93 | 97 |
| 8 | **1h** | 5-F | **3h** | 94 | 98 |
| 9 | **1i** | 5-Cl | **3i** | 78 | 98 |
| 10 | **1j** | 4-Br | **3j** | 89 | 99 |
| 11 | **1k** | 5-Br | **3k** | 97 | 99 |
| 12 | **1l** | 5-I | **3l** | 90 | 99 |
| 13 | **1m** | 6-Cl | **3m** | 83 | 98 |
| 14[e] | **1n** | 5-$CO_2$Me | **3n** | 54 | 98 |
| 15[e] | **1o** | 6-$CO_2$Me | **3o** | 37 | >99 |

[a] Reaction conditions: indole **1** (0.275 mmol), phthalimidomethylenemalonate **2** (0.25 mmol), $Cu(OTf)_2$ (10 mol%), **L2** (10 mol%), 1,4-dioxane/DME 10:1 (1.5 ml). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at room temperature. [e] The reaction was carried out for 72 h.

Based on the absolute configuration of the chiral centre in **3k** and on crystallographic data obtained by Evans and co-workers,[23] the *Si*-face attack of the indole on the intermediate complex of phthalimidomethylenemalonate **2** with $Cu(OTf)_2$/**L2** (Figure 4) can be assumed to take place from the side of the phthalimide fragment. When using the same catalytic system and oxygen-containing solvents in the reaction with dialkylbenzylidenemalonate, indole is likely to attack in a similar manner since an (*S*)-isomer[24] is formed. Perhaps π-π stacking the indole aromatic system with the benzene ring of the substrate takes place, and therefore this attack direction (*Si*-face) becomes preferable to the *Re*-face attack from the hydrogen side. The *Si*-face attack from the hydrogen side and *Re*-face attack from the side of the aromatic substituent are blocked by isopropyl groups of the bis(oxazoline) ligand.

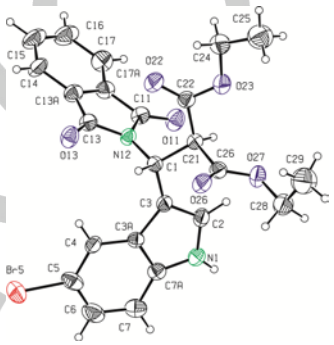



**Figure 3.** X-ray crystal structure of **3k** with displacement ellipsoids drawn at the 30% probability level. H atoms are presented as small spheres of arbitrary radius.

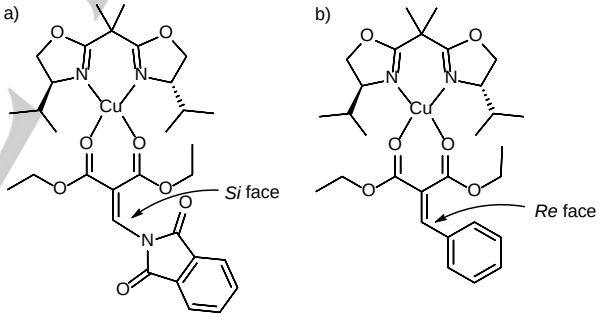
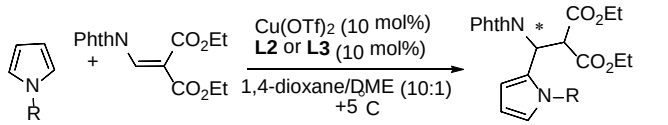



**Figure 4.** Proposed stereochemical models for the approach of indole to the a) phthalimidomethylenemalonate **2** and b) diethyl benzylidenemalonate, coordinated to $Cu(OTf)_2$/**L2** complex.

Encouraged by the results described above, we attempted to extend the method to the Friedel-Crafts alkylation of pyrroles with phthalimidomethylenemalonate **2** to obtain pyrrole analogues of $\beta^3$-tryptophan. The unsubstituted pyrrole **10a** and *N*-methylpyrrole **10b** were tested under the optimized conditions (Scheme 4). To avoid the formation of disubstituted pyrrole as a side-product, 10 equiv of **10a** and **10b** were used. The addition of pyrrole **10a** to substrate **2** led to product **11a** in high yield (90%) and moderate enantioselectivity (55% *ee*) within 24 h. The reaction of *N*-methylpyrrole with **2** did not run to completion even after 48 h. In this instance, product **11b** was obtained in good yield (83%), but with poor enantiomeric excess (12% *ee*). It is known that the enantioselectivity of Friedel-Crafts asymmetric

reactions of pyrroles is usually lower than indoles, for example, in the reaction with benzylidenemalonates[17a,i] and ethenetricarboxylates,[25] probably because of the smaller size of pyrrole molecules. However, the use of more sterically hindered ligand *t*BuBox (**L3**) instead of **L2** allowed us to increase the enantioselectivity of the reaction with pyrrole **10a** to 82%, albeit in slightly lower yield (80%).




**10a,** R=H **2** 24h **11a**

90% yield, 55% *ee* (with **L2**)
80% yield, 82% *ee* (with **L3**)

**10b**, R=Me 48h **11b**

83% yield, 12% *ee* (with **L2**)

**Scheme 4.** Enantioselective Friedel-Crafts reaction of pyrroles **10a**,**b** with phthalimidomethylenemalonate **2**.

## Conclusions

In conclusion, we have demonstrated the enantioselective Friedel-Crafts alkylation of indoles and pyrroles with protected aminomethylenmalonate to afford $\beta^3$-amino acid derivatives. Different amino-protective groups have been investigated. However, only the use of phthaloyl-protected aminomethylenmalonate allowed the desired products to be obtained. The reactions were performed in the presence of commercially available copper (II) triflate and *i*PrBox ligand under mild conditions. Friedel-Crafts alkylation products of various indoles were obtained in high yields with excellent enantioselectivity. Pyrroles reacted with phthalimidomethylenemalonate **2** under the same conditions also in high yields, but with low to moderate enantiomeric excess. The good enantioselectivity in the reaction with pyrrole was achieved using $Cu(OTf)_2$/*t*BuBox complex as a catalyst. The amino group deprotection step demands additional studies and is in progress in our laboratory.

## Experimental Section

**General Procedure for the enantioselective Friedel-Crafts alkylation of indoles 1a–o with phthalimidomethylenmalonate 2**.

A screw-top glass vial with a magnetic stir bar was charged with $Cu(OTf)_2$ (9.0 mg, 0.025 mmol, 10 mol%) and the solution of *i*PrBox ligand **L2** (6.7 mg, 0.025 mmol, 10 mol%) in a 1,4-dioxane/DME 10:1 mixture (1.5 ml) was added. The reaction mixture was stirred for 15 min followed by the addition of phthalimidomethylenmalonate **2** (79.3 mg, 0.25 mmol). The stirring was continued for 15 min, after that the resulting mixture was cooled to +5 °C and appropriate indole **1a**–**o** (0.275 mmol) was added. Then the reaction mixture was stirred at +5 °C for 48 or 72 h (for indoles **1n** and **1o** only), filtered through a plug of silica gel with EtOAc/$CH_2Cl_2$ (1:1) flushing, and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography to afford the desired product.

## Acknowledgements

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**Keywords:** amino acids • asymmetric catalysis • copper • enantioselectivity • indoles

[1] "β-Amino Acids in Natural Products": P. Spiteller, F. von Nussbaum in *Enantioselective Synthesis of β-Amino Acids* (Eds.: E. Juaristi, V. A. Soloshonok), John Wiley & Sons, Inc., Hoboken, **2005**, pp. 19–91; b) "*β*-Amino Acids in Nature": F. von Nussbaum, P. Spiteller in *Highlights in Bioorganic Chemistry: Methods and Applications* (Eds.: C. Schmuck, H. Wennemers), Wiley-VCH, Weinheim, **2004**, pp. 63–89; c) "*β*-Amino Acid Biosynthesis": P. Spiteller in *Amino Acids, Peptides and Proteins in Organic Chemistry*, Vol.1 (Ed.: A. B. Hughes), Wiley-VCH, Weinheim, **2009**, pp. 119–161; d) F. Kudo, A. Miyanaga, T. Eguchi, *Nat. Prod. Rep.*, **2014**, *31*, 1056–1073.

[2] a) K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38–69; *Angew. Chem. Int. Ed.* **1994**, *33*, 15–44; b) D. G. I. Kingston, *Chem. Commun.* **2001**, 867–880.

[3] a) M. Ishizuka, T. Masuda, N. Kanbayashi, S. Fukasawa, T. Takeuchi, T. Aoyagi, H. Umesawa, *J. Antibiot.* **1980**, *33*, 642–652; b) T. Koya, J. Narita, S. Honda and T. Abo, *Biomed. Res.* **1999**, *20*, 161–167; c) X. Chen, N. Li, S. Wang, N. Wu, J. Hong, X. Jiao, M. J. Krasna, D. G. Beer, C. S. Yang, *J. Natl. Cancer Inst.* **2003**, *95*, 1053–1061.

[4] D. L. Boger, H. Cai, *Angew. Chem.* **1999**, *111*, 470–500; *Angew. Chem. Int. Ed.* **1999**, *38*, 448–476.

[5] a) A. Fleming, *Br. J. Exp. Pathol.* **1929**, *10*, 226–236; b) D. J. Waxman, J. L. Strominger, Annu. Rev. Biochem. **1983**, *52*, 825–869; c) "140 – β-lactam antibiotics": R. R. Watkins, R. A. Bonomo in *Infectious Diseases*, Vol. 2 (Eds.: J. Cohen, W. Powderly, S. Opal), **2017**, Elsevier, pp. 1203–1216.e2; d) R. P. Elander, *Appl. Microbiol. Biotechnol.* **2003**, *61*, 385–392; e) H. S. Sader, R. N. Jones, *Antimicrob. Newsl.* **1992**, *8*, 75–84; f) A. R. Ribeiro, B. Sures, T. C. Schmidt, *Environ. Pollut. (Oxford, U. K.)* **2018**, *241*, 1153–1166.

[6] For selected examples, see: a) D. E. Mortenson, D. F. Kreitler, N. C. Thomas, I. A. Guzei, S. H. Gellman, K. T. Forest, *ChemBioChem* **2018**, *19*, 604–612; b) J.-S. Yu, H. Noda, M. Shibasaki, *Angew.Chem.* **2018**, *130*, 826–830; *Angew. Chem. Int. Ed.* **2018**, *57*, 818–822; c) M.-R. Lee, N. Raman, S. H. Gellman, D. M. Lynn, S. P. Palecek, *ACS Chem. Biol.* **2017**, *12*, 2975–2980; d) C. Mayer, M. M. Müller, S. H. Gellman, D. Hilvert, *Angew. Chem.* **2014**, *126*, 7098–7101; *Angew. Chem. Int. Ed.* **2014**, *53*, 6978–6981; e) L. M. Johnson, S. Barrick, M. V. Hager, A. McFedries, E. A. Homan, M. E. Rabaglia, M. P. Keller, A. D. Attie, A. Saghatelian, A. Bisello, S. H. Gellman, *J. Am. Chem. Soc.* **2014**, *136*, 12848−12851; f) G. A. Lengyel, W. S. Horne, *J. Am. Chem. Soc.* **2012**, *134*, 15906–15913.

[7] For a review, see: M. P. Del Borgo, K. Kulkarni, M.-I. Aguilar, *Aust. J. Chem.* **2017**, *70*, 126−129.

[8] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173−180.

[9] For reviews, see: a) R. Gopalakrishnan, A. I. Frolov, L. Knerr, W. J. Drury III, E. Valeur, *J. Med. Chem.* **2016**, *59*, 9599−9621; b) C. Cabrele, T. A. Martinek, O. Reiser, Ł. Berlicki, *J. Med. Chem.* **2014**, *57*, 9718−9739; c) T. A. Martinek, F. Fülöp, *Chem. Soc. Rev.* **2012**, *41*, 687–702; d) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366–1375; e) C. M. Goodman, S. Choi, S. Shandler, W. F. DeGrado, *Nat. Chem. Biol*. **2007**, *3*, 252–262; f) D. L. Steer, R. A. Lew, P. Perlmutter, A. I. Smith, M.-I. Aguilar, *Curr. Med. Chem.* **2002**, *9*, 811–822; g) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232.

[10] For reviews, see: a) *Enantioselective Synthesis of β-Amino Acids* (Eds.: E. Juaristi, V. A. Soloshonok), John Wiley & Sons, Inc., Hoboken, **2005**; b) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, *25*, 117–128; c) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; d) "Recent Developments in the Synthesis of *β*-Amino Acids": Y. Bandala, E. Juaristi in *Amino Acids, Peptides and Proteins in Organic Chemistry*. *Vol.1 – Origins and Synthesis of Amino Acids* (Ed. A. B. Hughes), **2009**, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, pp. 291–365; e) D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Grošelj, E. Zass, *Synthesis* **2009**, *1*, 1–32; f) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656–1691; g) L. Kiss, F. Fülöp, *Chem. Rev.* **2014**, *114*, 1116−1169; h) M. Ashfaq, R. Tabassum, M. M. Ahmad, N. A. Hassan, H. Oku, G. Rivera, *Med. Chem.* **2015**, *5*, 295–309; i) O. O. Grygorenko, *Tetrahedron* **2015**, *71*, 5169–5216.

[11] For selected reviews, see: a) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; b) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; c) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465; d) H. Wu, Y.-P. He, F. Shi, *Synthesis* **2015**, *47*, 1990–2016; e) A. H. Sandtorv, *Adv. Synth. Catal.* **2015**, *357*, 2403–2435; f) R. Dalpozzo, *Chem. Soc. Rev.* **2015**, *44*, 742–778; g) I. P. Beletskaya, A. D. Averin, *Curr. Organocatal.* **2016**, *3*, 60–83; h) J.-B. Chen, Y.-X. Jia, *Org. Biomol. Chem.* **2017**, *15*, 3550–3567.

[12] N. Pavlov, P. Gilles, C. Didierjean, E. Wenger, E. Naydenova, J. Martinez, M. Calmès, *J. Org. Chem.* **2011**, *76*, 6116–6124.

[13] J.-Q. Weng, Q.-M. Deng, L. Wu, K. Xu, H. Wu, R.-R. Liu, J.-R. Gao, Y.-X. Jia, *Org. Lett.* **2014**, *16*, 776−779.

[14] K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799–1803.

[15] G. Cardillo, L. Gentilucci, P. Melchiorre, S. Spampinato, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2755–2758.

[16] S. Harada, T. Sakai, K. Takasu, K. Yamada, Y. Yamamoto, K. Tomioka, *Tetrahedron* **2013**, *69*, 3264–3273.

[17] For selected examples, see: a) W. Zhuang, T. Hansen, K. A. Jørgensen, *Chem. Commun.* **2001**, 347–348; b) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030–9031; c) J. Zhou, Y. Tang, *Chem. Commun.* **2004**, 432–433; d) R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.*, **2006**, *8*, 6099-6102; e) A. Schätz, R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Chem. Eur. J.* **2008**, *14*, 7259–7265; f) Y.-J. Sun, N. Li, Z.-B. Zheng, L. Liu, Y.-B. Yu, Z.-H. Qin, B. Fu, *Adv. Synth. Catal.* **2009**, *351*, 3113–3117; g) Y. Liu, D. Shang, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 2055–2058; h) V. G. Desyatkin, M. V. Anokhin, V. O. Rodionov, I. P. Beletskaya, *Russ. J. Org. Chem.* **2016**, *52*, 1717−1727; i) M. V. Anokhin, M. N. Feofanov, A. D. Averin, I. P. Beletskaya, *ChemistrySelect* **2018**, *3*, 1388–1391.

[18] B. Brueckner, R. G. Boy, P. Siedlecki, T. Musch, H. C. Kliem, P. Zielenkiewicz, S. Suhai, M. Wiessler, F. Lyko, *Cancer Res*. **2005**, *65*, 6305–6311.

[19] The application of conventional phthalimide deprotection methods using hydrazine hydrate, ethane-1,2-diamine, $NaBH_4$/acetic acid did not allow to obtain corresponding derivatives with free amino group, and only mixture of unidentified products was formed in all cases. The attempts at first to decarboxylate product **3a** were also unsuccessful, since the elimination of phthalimide took place on heating or in the presence of inorganic bases.

[20] a) H. W. Dürbeck, L. L. Duttka, *Tetrahedron* **1973**, *29*, 4285–4290; b) G. O. Dudek, *J. Org. Chem.* **1965**, *30*, 548–552.

[21] a) L. Liu, J. Li, M. Wang, F. Du, Z. Qin, B. Fu, *Tetrahedron: Asymmetry* **2011**, *22*, 550–557; b) J. Wu, D. Wang, F. Wu, B. Wan, *J. Org. Chem.* **2013**, *78*, 5611−5617.

[22] CCDC-1564542 (for **3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] a) D. A. Evans, T. Rovis, M. C. Kozlowski, J. S. Tedrow, *J. Am. Chem. Soc.* **1999,** *121,* 1994–1995; b) D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573.

[24] J. Zhou, M.-C. Ye, Y. Tang, *J. Comb. Chem.* **2004**, *6,* 301–304.

[25] S. Yamazaki, Y. Iwata, *J. Org. Chem.* **2006**, *71*, 739–743.

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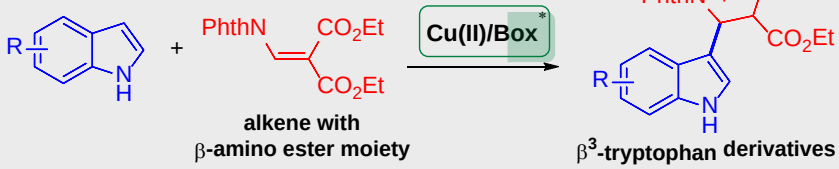


The straightforward way to highly enantioenriched $\beta^3$-amino acid derivatives using chiral copper complex catalyzed Friedel-Crafts reaction was developed.

*Dr. Elena A. Tarasenko, Ivan V. Shestakov, Dr. Victor B. Rybakov, Prof. Dr. Irina P. Beletskaya **

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