Sustainable Strategies for Site-Selective C–H Functionalizations of N-Heterocycles

Dissertation

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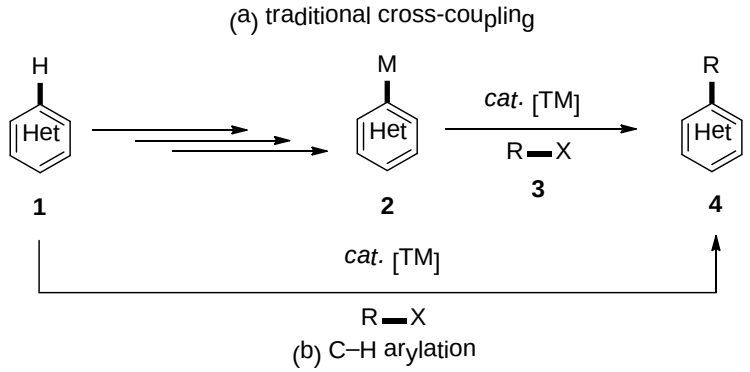
Contents

1 Introduction

Nitrogen-containing heterocycles are present in a variety of chemical compounds, ranging from pharmaceutical and agrochemical agents to diverse organic dyes.[1] Therefore, numerous efforts have been made to develop efficient and convenient methods for the formation of substituted heteroarenes.[2]

The traditional transition metal-catalyzed cross-coupling of organometallics **2** (M = MgX, ZnX, BR_2, SnR_3, SiR_3, etc.) and organic (pseudo)halogenides **3** has emerged as a powerful tool to achieve new C–C bond formations (Scheme 1).[3]



Scheme 1: Traditional cross-coupling *versus* C–H arylation.

In spite of these advances, drawbacks of transition metal-catalyzed cross-coupling reactions continue to be remarkable. Substrates need to be prefunctionalized to the organometallics **2** through time-consuming and economically inefficient multi-step transformations, and stoichiometric amounts of metal salts as by-products are formed during these reactions. To avoid these disadvantages and to streamline organic syntheses, catalytic C–H

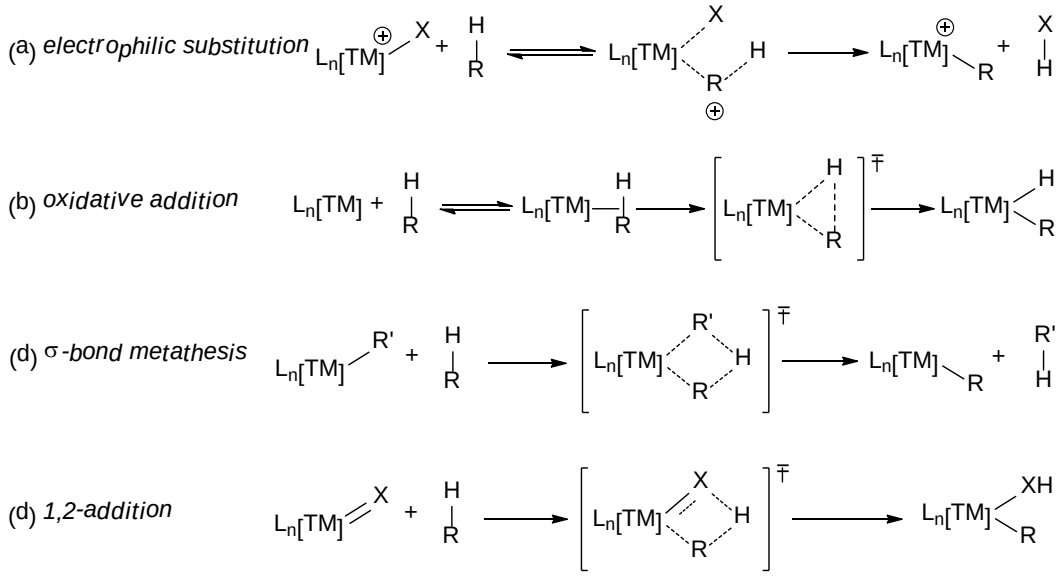
[1] (a) M. U. Schmidt, R. E. Dinnebier, H. Kalkhof, *J. Phys. Chem. B* **2007**, *111*, 9722–9732; (b) P. Goupy, A.-B. Bautista-Ortin, H. Fulcrand, O. Dangles, *J. Agric. Food Chem.* **2009**, *57*, 5762–5770; (c) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563–639; (d) R. Dua, S. Shrivastava, S. K. Sonwane, S. K. Srivastava, *Advan. Biol. Res.* **2011**, *5*, 120–144.

[2] (a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469; (b) L. Djakovitch, N. Batail, M. Genelot, *Molecules* **2011**, *16*, 5241–5267; (c) I. Hachiya, I. Mizota, M. Shimizu, *Heterocycles* **2012**, *85*, 1017–1043; (d) A. Majumder, R. Gupta, A. Jain, *Green Chem. Lett. Rev.* **2013**, *6*, 151–182; (e) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1–35; (f) A. Dhakshinamoorthy, H. Garcia, *Chem. Soc. Rev.* **2014**, *43*, 5750–5765.

[3] (a) *Metal-Catalyzed Cross-Coupling Reactions*; F. Diederich, P. J. Stang, Eds.; Wiley-VCH: New York, **1998**; (b) *Transition Metals for Organic Synthesis*; M. Beller, C. Bolm, Eds.; Wiley-VCH: Weinheim, **2004**.

functionalization has been developed as an excellent alternative, which has been intensively investigated during last ten years.[4]

An obvious challenge for these C–H functionalizations is the activation of inert C–H bonds. To overcome this challenge, a deep insight into the mechanism of the elementary C–H bond metalation step would be helpful.



Scheme 2: Possible mechanisms for insertion of a transition metal into a C–H bond.

Typically, four possible modes of action could be envisioned (Scheme 2).[5] The first pathway (a) is the electrophilic substitution often occurring with electron-deficient late transition metals, such as Pd^{2+}, Pt^{2+} or Pt^{4+}. For the electron-rich, low-valent complex of the late transition metal (Fe, Pd, Ru, Ir), the oxidative addition (b) of a C–H bond is largely preferred. Because the early transition metal with d^0-configuration cannot undergo the oxidative addition, *σ*-bond metathesis (c) becomes predominant here. The transition metal mediated C–H bond insertion can also proceed *via* 1,2-addition (d) to an unsaturated [TM]=X bond.

[4] For selected representative reviews on C–H activation, see: (a) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, 2833–2836; (b) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; (c) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; (d) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; (e) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802; (f) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal*. **2014**, *356*, 17–117; (g) R. Rossi, F. Bellina, M. Lessi, C. Manzini, L. A. Perego, *Synthesis* **2014**, *46*, 2833–2883; (h) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed*. **2014**, *53*, 74–100.

[5] (a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; (b) D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749–823.

In addition to these reaction pathways, more recent mechanistic studies demonstrate the existence of a continuum of electrophilic, ambiphilic and nucleophilic interactions at the C–H bond metalation step.[6] Furthermore, it is often found that a base is not a simple bystander regenerating the active catalyst, but that it is directly involved in the transition state of the C–H bond metalation.[7,8] These strongly indicate a novel mechanism, namely the base-assisted C–H bond metalation.6 A bidentate base, such as a carboxylate8 or a phosphinous acid,[9] binds to a transition metal and interacts with a C–H bond, resulting in a six-membered transition state (Figure 1). This intramolecular metalation pathway is coined as concerted metalation-deprotonation (CMD)[10] or ambiphilic metal ligand activation (AMLA).6[b,11] An additional mechanism referred to as internal electrophilic substitution (IES).6[b,12]

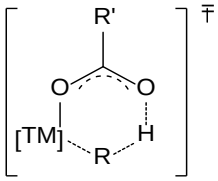


Figure 1: Base-assisted C–H bond metalation.

Another challenge for the direct C–H bond functionalization is the presence of numerous similarly reactive C–H bonds in the substrate. In order to regioselectively functionalize a specific C–H bond, a commonly exploited strategy is the installation of a removable directing group (Scheme 3).[13] By elaborately designing the directing group, *ortho*-[14] und *remote*-C–H

[6] (a) D. H. Ess, W. A. Goddard III, R. A. Periana, *Organometallics* **2010**, *29*, 6459–6472; (b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

[7] (a) J. C. Gaunt, B. L. Shaw, *J. Organomet. Chem.* **1975**, *102*, 511–516; (b) V. I. Sokolov, L. L. Troitskaya, O. A. Reutov, *J. Organomet. Chem.* **1979**, *182*, 537–546; (c) D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton, D. R. Russell, *Dalton Trans.* **2003**, 4132–4138.

[8] L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281–295.

[9] L. Ackermann, *Synthesis* **2006**, 1557–1571.

[10] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

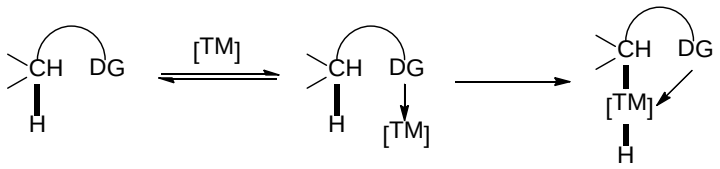
[11] Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831.

[12] (a) J. Oxgaard, W. J. Trenn III, R. J. Nielsen, R. A. Periana, W. A. Goddard III, *Organometallics* **2007**, *26*, 1565–1567; (b) D. Conner, K. N. Jayaprakash, T. R. Cundari, T. B. Gunnoe, *Organometallics* **2004**, *23*, 2724–2733; (c) J. R. Webb, T. BolaÇo, T. B. Gunnoe, *ChemSusChem* **2011**, *4*, 37–49.

[13] For reviews on removable directing groups, see: (a) C. Wang, Y. Huang, *Synlett* **2013**, *24*, 145–149; (b) F. Zhang, D. R. Spring, *Chem. Soc. Rev*. **2014**, *43*, 6894–6905.

[14] (a) *Modern Arylation Methods*; L. Ackermann, Ed.; Wiley-VCH: Weinheim, **2009**; (b) D. Takeda, M. Yamashita, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2011**, *40*, 1015–1017; (c) T.

bond functionalization[15] can be achieved.



Scheme 3: Site-selective intermolecular C–H metalations through the use of directing groups (DG).

Furthermore, a variety of reactions exploiting appropriate ligands,[16] electron-rich substrates,[17] or the kinetic C–H bond acidity[18] among others have been developed to enhance the site-selectivity.

1.1 Transition Metal-Catalyzed C–H Alkynylations of Azoles

Since *Sonogashira* discovered the pioneering cross-coupling reaction between terminal acetylene and vinyl-, or arylhalogenide in the presence of $(PhP_3)_2PdCl_2$ and the cocatalyst CuI,[19] the obstacle to the mild and convenient synthesis of unsymmetrical acetylenes was remarkably overcome. Besides Sonogashira-type reactions, the site-selective direct C–H alkynylation of azoles as a viable alternative could be realized by exploiting significantly different kinetic C–H bond acidities between the ubiquitous C–H bonds present in the azoles compounds, as indicated by their pK_a values (Figure 2).[20]

Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286–5287.

[15] (a) D. Leow, G. Li, T. Mei, J.-Q. Yu, *Nature*, **2012**, *486*, 518–522; (b) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884; (b) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 10807–10813.

[16] (a) B. Glover, K. A. Harvey, B. Liu, M. J. Sharp, M. Tymoschenko, *Org. Lett.* **2003**, *5*, 301–304; (b) T. W. Lyons, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 4455–4464.

[17] (a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473; (b) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748–11749.

[18] (a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021; (b) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1607; (c) L. Ackermann, S. Fenner, *Chem. Commun.***2011**, *47*, 430–432.

[19] (a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; (b) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.

[20] K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568–1576.

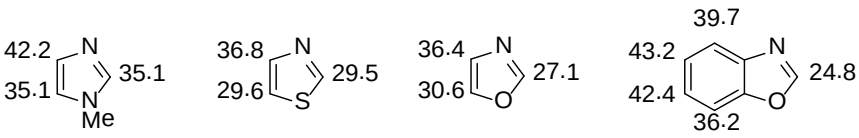
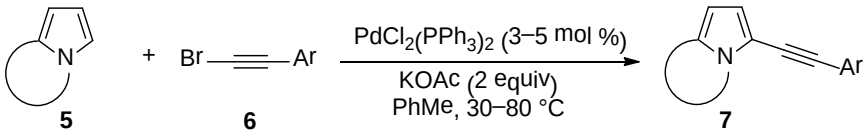


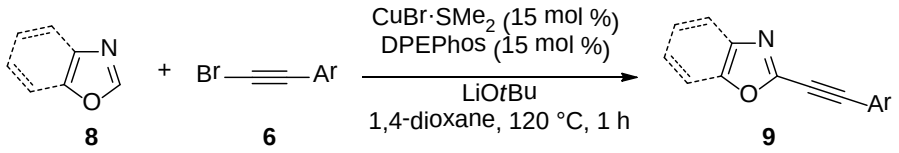
Figure 2: Calculated pK_a values of azoles.

Compared to significant advances in transition metal-catalyzed C–H arylations and alkenylations of azoles, C–H alkynylations of heteroarenes received relatively low attention until *Gevorgyan* reported a palladium-catalyzed direct alkynylation of *N*-fused heteroarene **5** with haloacetylene **6** (Scheme 4).[21a]



Scheme 4: Palladium-catalyzed direct alkynylations of *N*-fused heterocycles **5**.

Later, *Piguel*'s work demonstrated that copper complexes were also capable of efficiently catalyzing direct C2-alkynylations of oxazoles **8** in the presence of DPEPhos as the ligand and LiO*t*Bu as the base (Scheme 39).[22]



Scheme 5: Cu-catalyzed direct alkynylations of oxazoles **100**.

Despite the great tolerance of haloacetylenes **6** in the direct alkynylations, these electrophiles are instable. The moisture-stable *gem*-dihaloalkenes seem to be a viable candidate for replacing haloacetylenes.[23] As reported by *Piguel* (Scheme 6),[24] *gem*-dibromoalkene **10** could oxidatively add to the heteroarylcopper species **12** generated from **8** and **11** as well as LiO*t*Bu, and then reductively couple with the heteroaryl group to form alkenyloxazole **14**, which was further converted to alkynylated product **9** by elimination of a molecular HBr (Scheme 6, path A). Alternatively, *gem*-dibromoalkene **10** could first be transformed to bromoacetylene **6**, and

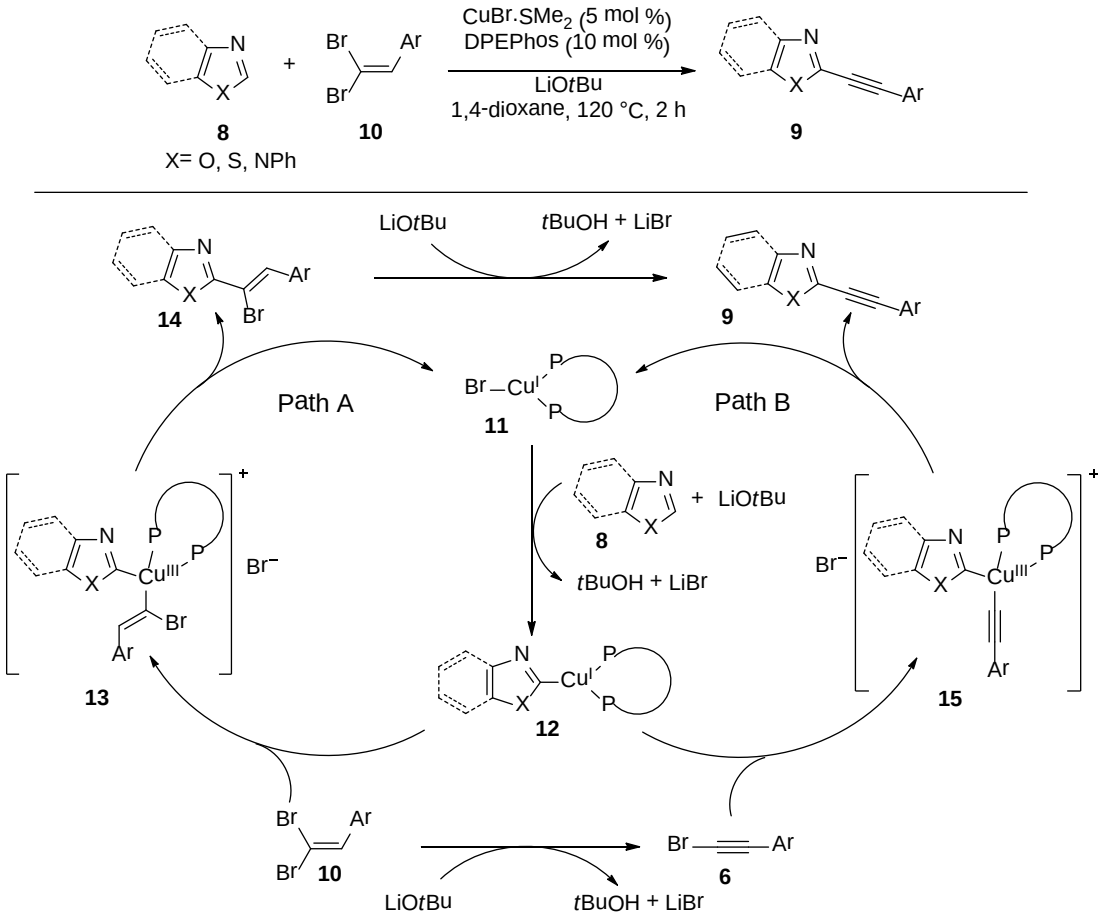
[21] (a) I. V. Seregin, V. Ryabova, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 7742–7743. For the further development of this approach, see: (b) S. H. Kim, S. Chang, *Org. Lett.* **2010**, *12*, 1868–1871.

[22] F. Besselièvre, S. Piguel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9553–9556.

[23] G. Chelucci, *Chem. Rev.* **2012**, *112*, 1344–1462.

[24] B. P. Berciano, S. Lebrequier, F. Besselièvre, S. Piguel, *Org. Lett.* **2010**, *12*, 4038–4041.

the subsequent oxidative addition and the reductive elimination would lead to desired product **9** *via* the intermediate **15** (path B). Given that no alkenyloxazole **14** was observed, *Piguel* tended to regard the path B as more likely. Notably, LiO*t*Bu as a strong base was necessary for both the deprotonation of oxazole **8** and the conversion of the alkenyl moiety to the alkynyl functionality.

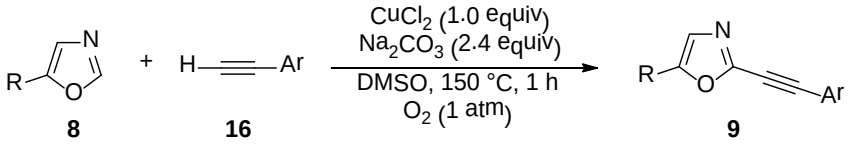


Scheme 6: Copper-catalyzed direct alkynylations of oxazoles **8** with *gem*-dibromoalkenes **10**.

In addition to Sonogashira-type or to direct alkynylations, the approach *via* dehydrogenative oxidative alkynylation provides a straightforward access to diverse alkynylated heterocycles as well. In 2010, *Miura* reported on the $CuCl_2$-mediated direct alkynylation of oxazoles **8** with terminal alkynes **16** and oxygen as the terminal oxidant (Scheme 7).[25] Despite the stoichiometric exploitation of the transition metal in this work, it has laid the foundation for further more convenient catalytic protocols utilizing nickel,[26] palladium[27] and gold[28]

[25] M. Kitahara, K. Hirano, H. Tsurugi, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 1772–1775.
[26] N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358–2361.
[27] (a) S. H. Kim, J. Yoon, S. Chang, *Org. Lett.* **2011**, *13*, 1474–1477; (b) F. Shibahara, Y. Dohke,

complexes as the catalysts.



Scheme 7: Oxidative alkynylation of oxazoles **8**.

1.2 Transition Metal-Catalyzed C–H Arylations of Indoles

Indole is one of the most frequently appearing nitrogen heterocycles in nature. Because of its immense structural variety, indole is of especial importance in the field of pharmaceutics and functional materials.[29] Besides well-known traditional methods, such as *Fischer*[30] or *Larock*[31] indole syntheses as well as cyclizations,[32,33] the C–H arylation has emerged as a highly powerful tool for the synthesis of arylated indoles.[34]

1.2.1 Palladium-Catalyzed C–H Arylations of Indoles

Due to the electron density distribution, the C(2)–H and the C(3)–H bond of electron-rich indoles are more susceptible to the direct palladium-catalyzed arylation as compared the aromatic C–H bonds in these molecules.

During the pioneering investigation of palladium-catalyzed direct C–H bond functionalizations of indoles **17** with chloropyrazines **18**, *Ohta* observed that a protecting

T. Murai, *J. Org. Chem.* **2012**, *77*, 5381–5388.

[28] T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512–1513.

[29] (a) A. P. Kozikowski, D. Ma, J. Brewer, S. Sun, E. Costa, E. Romeo, A. Guidotti, *J. Med. Chem.* **1993**, *36*, 2908–2920; (b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2910; (c) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620–6662.

[30] B. Robinson, *The Fischer Indole Synthesis*, Wiley & Sons: Chichester, **1982**.

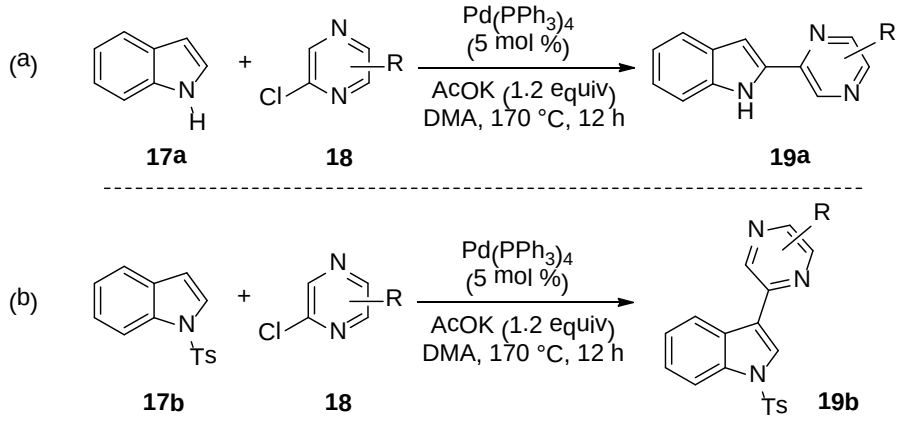
[31] (a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690; (b) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680.

[32] (a) K. Iritani, S. Matsubara, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 1799–1802. Reviews: (b) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469–6480; (c) L. Djakovitch, N. Batail, M. Genelot, *Molecules* **2011**, *16*, 5241–5267; (d) L. Ackermann, *Synlett* **2007**, 507–526.

[33] (a) L. Ackermann, *Org. Lett.* **2005**, *7*, 439–442; (b) L. T. Kaspar, L. Ackermann, *Tetrahedron*, **2005**, *61*, 11311–11316; (c) L. Ackermann, S. Barfüßer, H. K. Potukuchi, *Adv. Synth. Catal.* **2009**, *351*, 1064–1072; (d) L. Ackermann, R. Sandmann, M. V. Kondrashov, *Synlett* **2009**, 1219–1222; (e) L. Ackermann, R. Sandmann, M. Schinkel, M. V. Kondrashov, *Tetrahedron* **2009**, *65*, 8930–8939; (f) L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764–767; (g) W. Song, L. Ackermann, *Chem. Commun.* **2013**, *49*, 6638–6640.

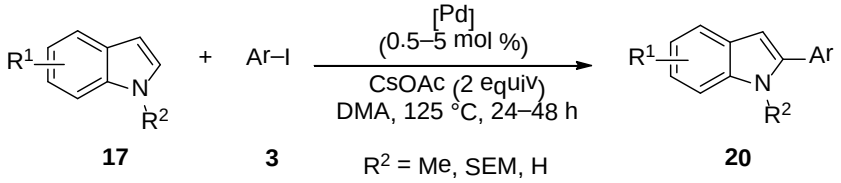
[34] (a) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673–714; (b) G. Broggini, E. M. Beccalli, A. Fasana, S. Gazzola, *Beilstein J. Org. Chem.* **2012**, *8*, 1730–1746.

group on the indole nitrogen can significantly affect the C3/C2-site-selectivity (Scheme 8). While the reaction of free (NH)-indole **17a** exclusively proceeded affording the C2-functionalized product **19a** (Scheme 8a),[35] a tosyl group as an electron-withdrawing substituent on the indole nitrogen switched the selectivity towards the formation of the C3-arylated indole **19b** (Scheme 8b).[36]



Scheme 8: Palladium-catalyzed arylation of indoles **5** with chloropyrazines **6**.

After two decades, *Sames* applied similar reaction conditions for the arylation of indoles **17** with iodoarenes **3** and obtained C2-arylated heterocycles **20** in moderate to good yields (Scheme 9).[37] Notably, *Sames* also mentioned that the C3-regioisomer became the major product, when a sterically demanding iodoarene **3**, such as 1-iodo-2-[(4-methoxybenzyl)-oxy]benzene (**3a**), was employed.



Scheme 9: C2-Arylations of indoles.

In 2008, *Larrosa* disclosed a convenient, mild and high yielding method for the palladium-catalyzed phosphine-free direct arylation of *N*-methylindole **17c** (Scheme 10).[38]

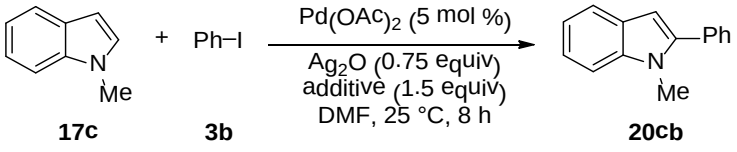
[35] Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles* **1985**, *23*, 2327–2333.

[36] Y. Akita, Y. Itagaki, S. Takizawa, A. Ohta, *Chem. Pharm. Bull.* **1989**, *37*, 1477–1480.

[37] (a) B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897–2900; (b) B. B. Touré, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979–1982; (c) X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476–1479.

[38] N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927.

Ag_2O as the base reacted with arylpalladium complex to provide a more electrophilic palladium species, likely *via* precipitation of silver iodide. Thus, the resulting highly reactive palladium species reinforced the subsequent coordination of indole and the reductive elimination. Moreover, it was observed that the p*K*a of the stoichiometrically added carboxylic acid correlated closely with the catalytic reactivity, with *o*-nitrobenzoic acid (**21**) providing optimal results.



17c **3b** **20cb**

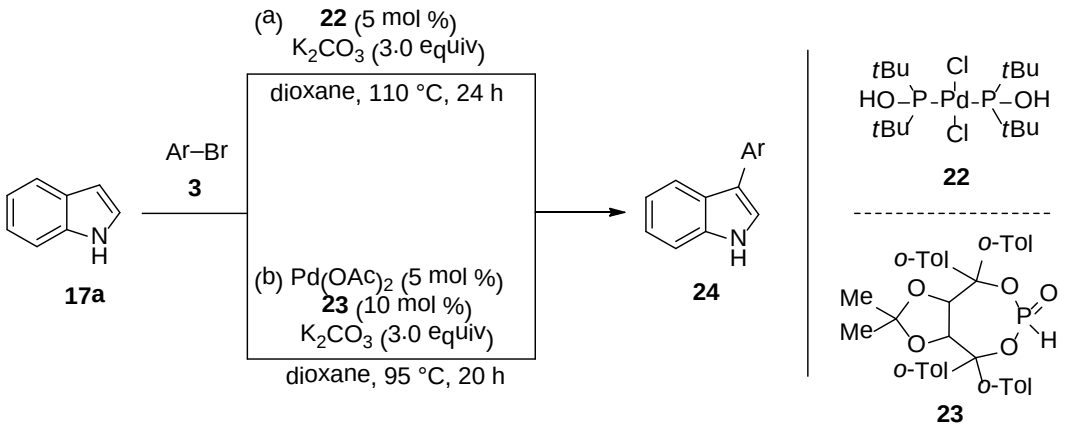
additive	conversion [%] (GC)
---	1
CH_3CO_2H	49
o-$MeOC_6H_4CO_2H$	13
p-$O_2NC_6H_4CO_2H$	81
o-$O_2NC_6H_4CO_2H$ (**21**)	>99

Scheme 10: Palladium-catalyzed phosphine-free direct arylations of indoles **17c**.

As mentioned above, palladium-catalyzed C–H bond functionalizations were generally observed with C2-regioselectivity. In order to shift the regioselectivity to C3, a withdrawing protecting group on indolic nitrogen or sterically bulky arylating reagent is usually required.[34a] Besides this, a suitable ligand coordination in the palladium catalyst could also lead to the same result (Scheme 11). For instance, *Zhang* used the air-stable palladium/ phosphinous acid complex **22** as the catalyst for the reaction of indole **17a** with arylbromides **3**, which afforded 3-arylindoles **24** in moderate to good yields (Scheme 11a).[39] Moreover, *Ackermann* designed a palladium complex generated *in situ* from an air-stable heteroatom-substituted secondary phosphine oxide **23** (HASPO), and this resulted in a high C3-regioselectivity likewise (Scheme 11b).[40]

[39] Z. Zhang, Z. Hu, Z. Yu, P. Lei, H. Chi, Y. Wang, R. He, *Tetrahedron Lett.* **2007**, *48*, 2415–2419.

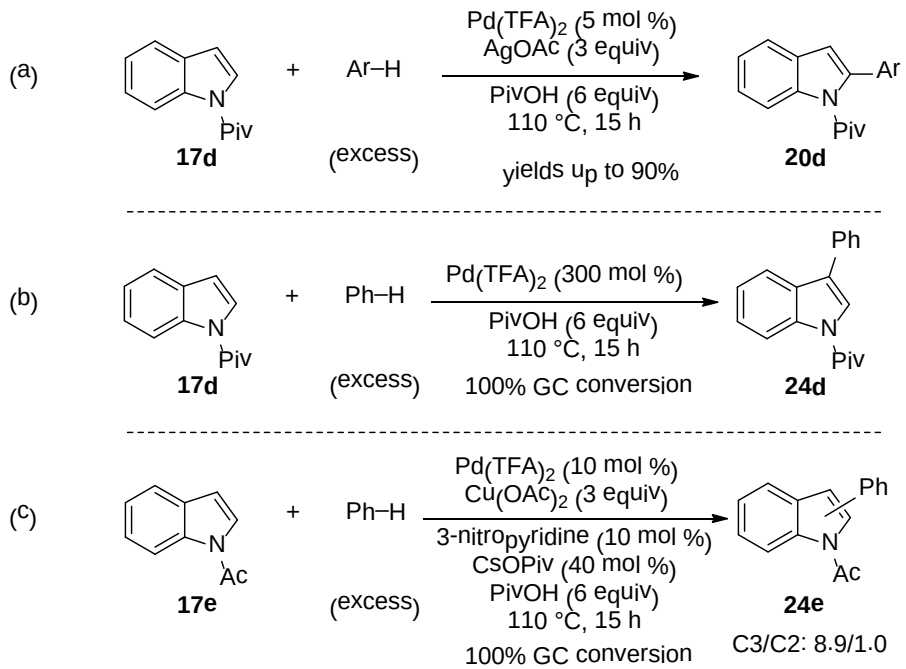
[40] L. Ackermann, S. Barfüßer, *Synlett* **2009**, 808–812.



Scheme 11: Palladium-catalyzed direct C3-arylations of indoles **17a**.

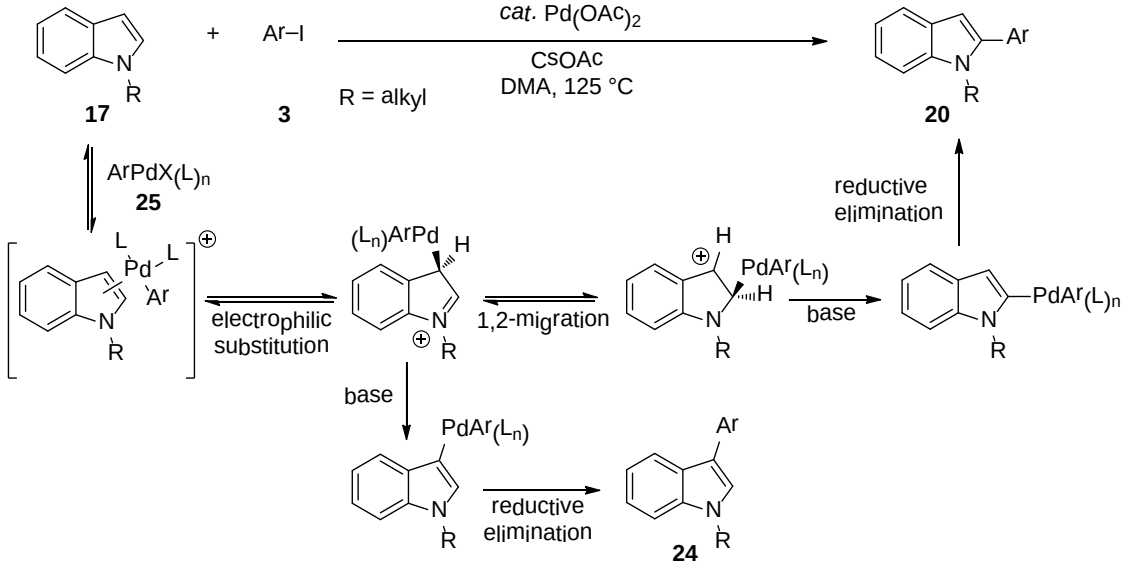
Following *Itahara*'s pioneering study,[41] *Fagnou* performed investigations on the oxidative direct arylations of indoles **17** with an excess of arene (Scheme 12).[42] 2-Arylindole **20d** was produced by employing $Pd(TFA)_2$, AgOAc and PivOH (Scheme 12a). When the $Pd(TFA)_2$ loading was increased from 5 to 300 mol % in the absence of AgOAc, only 3-phenylindole **24d** was obtained (Scheme 12b). Moreover, the replacement of AgOAc by $Cu(OAc)_2$ also gave rise to the C3-arylated regioisomer **24e** with a ratio of 8.9:1 (Scheme 12c). These results indicated that the C3/C2-regioselectivity was presumably related to the concentration of higher-order palladium clusters. While a catalytic quantity of the monomeric palladium species formed by carboxylate-induced cleavage of palladium clusters led to a selective functionalization of the C(2)–H bond, superstoichiometric quantities of $Pd(TFA)_2$ as well as the mixed palladium–copper intermediate clusters,[43] formed by the addition of $Cu(OAc)_2$, maintained a high concentration of palladium clusters and facilitated a site-selective C3-arylation.

[41] T. Itahara, *J. Chem. Soc., Chem. Commun.* **1981**, 254–255.
[42] D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073.
[43] (a) R. W. Brandon, D. V. Claridge, *J. Chem. Soc., Chem. Commun.* **1968**, 677–678; (b) O. D. Sloan, P. Thornton, *Inorg. Chim. Acta* **1986**, *120*, 173–175.



Scheme 12: Palladium-catalyzed oxidative direct arylations of indoles **17**.

As to the mechanism for palladium-catalyzed C2-arylations of indoles **17** with aryliodides **3**, *Sames* suggested a palladium(0)/palladium(II) catalytic cycle involving an initial electrophilic substitution of Ar-Pd^{II}-X species **25** at the C3 position and a subsequent 1,2-migration to C2 (Scheme 13), which was strongly supported by mechanistic studies including kinetic isotope effect (KIE) studies, intermolecular competition experiments and Hammett plots studies.[44]



Scheme 13: Possible reaction mechanism for the palladium-catalyzed C–H arylation of indole **17**.

[44] B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.

Meanwhile, *Sames* pointed out that the C3/C2-regioselectivity was strongly related to the reaction rates of the electrophilic substitution and the 1,2-migration, both of which were kinetically relevant and remarkably influenced by the size of the arylating reagents and metal-ligand complexes. If the reaction rate of the 1,2-migration was lower than those for the abstraction of the proton at the C3 position, the probability to obtain 3-arylindoles **24** increased.

1.2.2 Arylations of (Hetero)Arenes with Diaryliodonium Salts

1.2.2.1 Structure of Diaryliodonium Salts

Since *Hartmann* and *Meyer* first synthesized diaryliodonium salts **26** in 1894,[45] the air- and moisture-stable hypervalent iodine(III) compounds have received high attention due to their highly electrophilic nature and excellent leaving group ability of the aryliodonium moiety. They have been widely utilized in direct electrophilic arylations of various nucleophiles and in transition metal-catalyzed cross-coupling reactions.[46,47]

In general, hypervalent iodine(III) compounds $ArIL^1L^2$ exhibit pseudotrigonal bipyramidal structures and are roughly T-shaped at the iodine center, as shown in Figure 3. An aryl group and two electron lone pairs are equatorial in the λ^3-iodane, and two ligands L *trans* to each other are apical. In 1951, on the basis of molecular orbital theory, *Pimentel*[48] and *Rundle*[49] explained the structure and the electrophilic nature of λ^3-iodanes by utilizing the concept of a three-center-four-electron (3c-4e) bond for the L^1–I–L^2 moiety. The filled 5p orbital of the iodine atom interacts with the half-filled orbitals of the two ligands L to form three molecular orbitals: bonding, nonbonding and antibonding. The electron pair in the nonbonding

[45] C. Hartmann, V. Meyer, *Chem. Ber.* **1894**, *27*, 426–432.

[46] (a) *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*; V. V. Zhdankin, Ed.; John Wiley & Sons: Chichester West Sussex, **2014**; (b) *Iodine Chemistry and Applications*; T. Kaiho, Ed.; John Wiley & Sons: Hoboken, **2015**.

[47] For selected reviews on hypervalent iodine(III) chemistry: (a) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, 96, 1123–1178; (b) A. Varvoglis, *Tetrahedron* **1997**, *53*, 1179–1255; (c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523–2584; (d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358; (e) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070.

[48] G. C. Pimentel, *J. Chem. Phys.* **1951**, *19*, 446–448.

[49] R. J. Hach, R. E. Rundle, *J. Am. Chem. Soc.* **1951**, *73*, 4321–4324.

molecular orbital is delocalized to the two ligands, so that this L^1–I–L^2 hypervalent bond is highly polarized and makes iodine atom partially electropositive. Hence, more electronegative ligands such as hydroxide, carboxylate, are more likely to occupy the apical positions. Depending on the different electronegativity of the ligands, the polarization of the hypervalent bond can be symmetrical ($L^1 = L^2$) or unsymmetrical ($L^1 \neq L^2$).

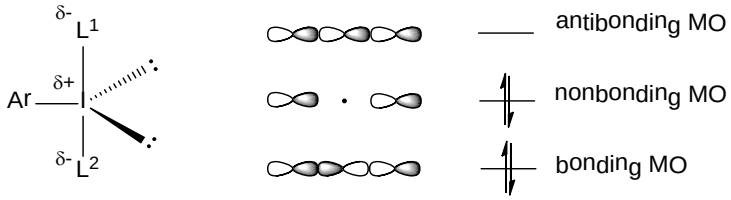
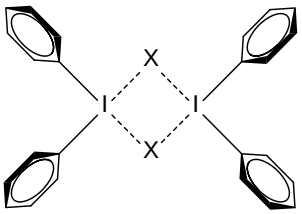


Figure 3: Molecular orbital description of the (3c-4e) bond in $ArIL_2$.

In 1977, *Alcock* and *Countryman* published a detailed X-ray crystal structure study of diphenyliodonium halides.[50] In solid state, the iodine-halogen bonds held two diphenyliodonium salt molecules together to form an anion-bridged dimer **27**. As shown in Figure 4, all I–C bonds are equally long (2.09 Å), and the I···Cl bond distance (3.09 Å) is much longer than the regular hypervalent I–Cl bond length of $PhICl_2$ (2.45 Å).[51] Because the halide is more electronegative than the aryl group, the electrons in the hypervalent bond are mostly concentrated on the halogen atom, and the hypervalent bond in this case tends to display an ionic property.[46a]



27

	Bond length I–X	Angle Ar–I–Ar
X = Cl:	3.09 Å	92.6 °
X = Br:	3.25 Å	93.2°
X = I:	3.44 Å	91.8°

Bond length I–C(sp^2): 2.09 Å

Figure 4: Structure of dimeric diphenyliodonium halides **27**.

[50] N. W. Alcock, R. M. Countryman, *J. Chem. Soc., Dalton Trans.* **1977**, 217–219.
[51] E. M. Archer, T. G. D. Van Schalkwyk, *Acta Cryst.* **1953**, *6*, 88–92.

1.2.2.2 Transition Metal-Catalyzed Arylations of (Hetero)Arenes

After Crabtree employed iodobenzene diacetate (**28**) to accomplish palladium-catalyzed acetoxylation of arenes **1** in 1996,[52] a variety of highly efficient and site-selective catalytic methods for the oxidative C–H acetoxylation or hydroxylation has been developed.[53,54]

Thereafter, the transition metal-catalyzed arylations of (hetero)arenes with diaryliodonium salts **26** has attracted increasing attention. In 2005, *Sanford* published a directing group-assisted palladium-catalyzed direct arylation of arenes **29** (Scheme 14).[55a] A range of directing groups proved to be viable for the *ortho*-monophenylations. And the diphenyliodonium salt (**26a**) was regarded as the best phenylating reagent in comparison to PhI or PhOTf, which both failed to provide desired product **30** under the same reaction conditions. Notably, the addition of 500 equiv. of mercury, a potent poison for heterogeneous catalysis,[56] did not decrease the catalyst activity, indicating this reaction to proceed more likely *via* a homogenous palladium(II)/palladium(IV) catalytic cycle rather than through a traditional palladium(0) nanoparticle/palladium(II) one. Furthermore, the introduction of radical scavengers like hydroquinone monomethyl ester (MEHQ) or free radical galvinoxyl did not affect the reaction progress, suggesting that the reactions proceeded without participation of free radical intermediates.

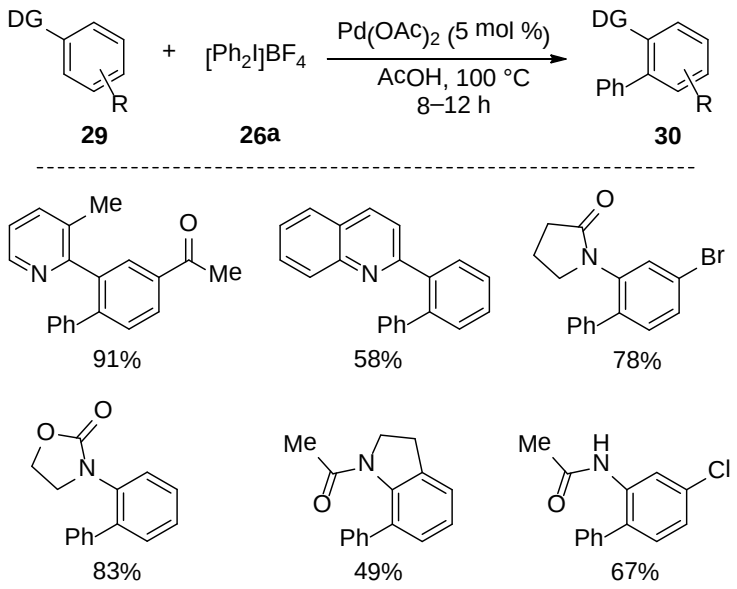
[52] T. Yoneyama, R. H. Crabtree, *J. Mol. Catal. A* **1996**, *108*, 35–40.

[53] (a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; (b) S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912–4924; (c) V. S. Thirunavukkarasu, S. I. Kozhushkov, L. Ackermann, *Chem. Commun.* **2014**, *50*, 29–39.

[54] (a) V. S. Thirunavukkarasu, J. Hubrich, L. Ackermann, *Org. Lett.* **2012**, *14*, 4210–4213; (b) V. S. Thirunavukkarasu, L. Ackermann, *Org. Lett.* **2012**, *14*, 6206–6209; (c) F. Yang, L. Ackermann, *Org. Lett.* **2013**, *15*, 718–720; (d) W. Liu, Ackermann, *Org. Lett.* **2013**, *15*, 3484–3486; (e) F. Yang, K. Rauch, K. Kettelhoit, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 11285–11288.

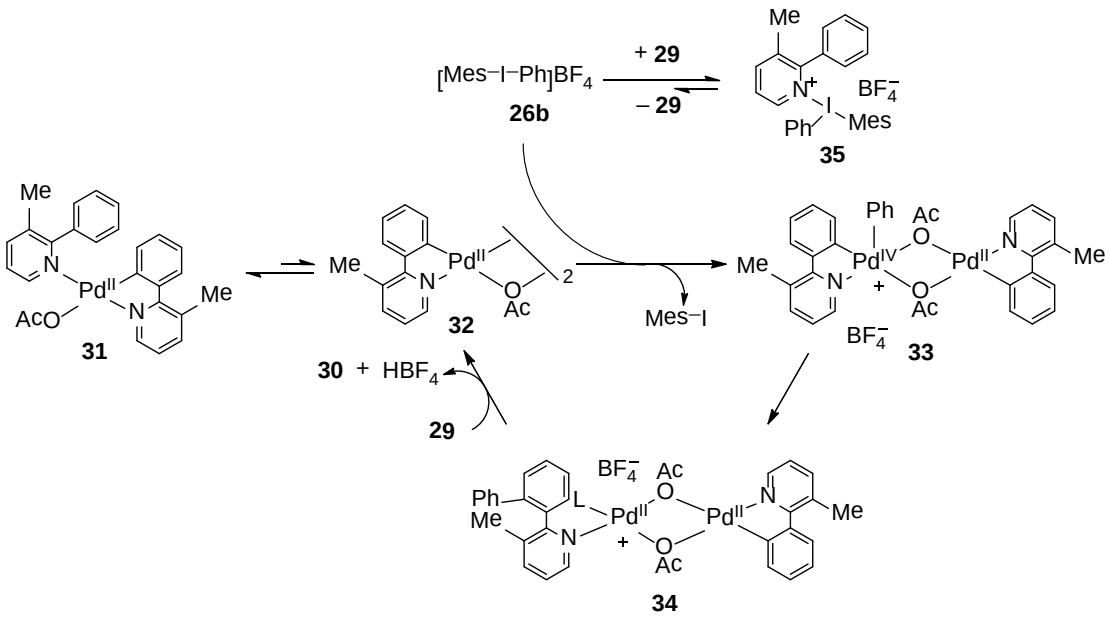
[55] (a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. For selected recent communications, see: (b) L. Y. Chan, L. Cheong, S. Kim, *Org. Lett.* **2013**, *15*, 2186–2189; (c) T. E. Storr, M. F. Greaney, *Org. Lett.* **2013**, *15*, 1410–1413; (d) Z. Wu, S. Chen, C. Hu, Z. Li, H. Xiang, X. Zhou, *ChemCatChem* **2013**, *5*, 2839–2842.

[56] M. R. Eberhard, *Org. Lett.* **2004**, *6*, 2125–2128.



Scheme 14: palladium-catalyzed arylations with diaryliodonium tetrafluoroborates (**26a**).

Based on in-depth mechanistic studies, a palladium(II)/palladium(IV) catalytic cycle was proposed (Scheme 15).[57]



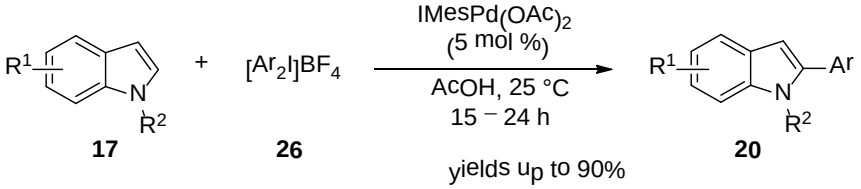
Scheme 15: Proposed mechanism for C–H arylation *via* binuclear palladium complex **32**.

After the insertion into the C–H bond, palladium forms the monomeric palladium(II) complex **31**, which is in equilibrium with the active binuclear species **32**. Subsequently, a phenyl group from the unsymmetrical diaryliodonium salt **26b** oxidatively adds to the palladium species **32** to form the complex **33**. The following reductive elimination in **33** and the final ligand

[57] N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.

exchange with participation of **29** provided the desired product **30**, thus finishing this catalytic cycle. Notably, the authors observed that within this pathway the diaryliodonium salt **26b** readily and reversible reacts with the 2-phenylpyridine (**29**) to form a λ^3-iodane compound **35** possessing an I–N bond.[58]

The same palladium(II)/palladium(IV) catalytic mechanism can be assumed for the direct C–H bond arylation of indoles **17** with diaryliodonium salts **26**.[59] Due to the highly nucleophilic property of electron-rich indoles, the reactions can smoothly proceed at ambient temperature in the presence of $IMesPd(OAc)_2$, affording C2-arylated indoles **20** (Scheme 16).



Scheme 16: Palladium-catalyzed direct C2-arylation of indoles **5**.

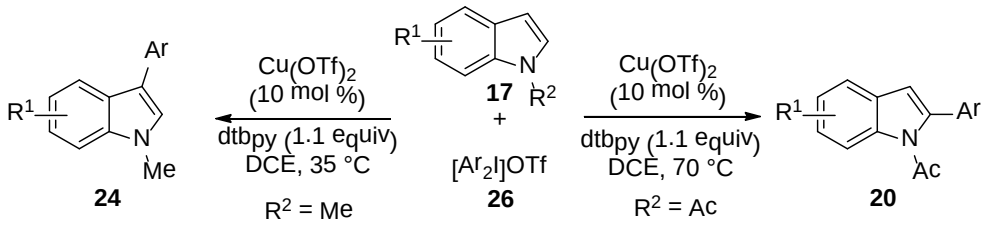
While palladium catalysts were broadly used in the arylation of (hetero)arenes,[4f,55b–e] the value of copper catalysts, which offer an economic advantage, was rarely appreciated.[60,61] *Gaunt* proposed of the copper(III) as a highly electrophilic d^8-configured metal, which would enable the C–H functionalizaitons.[60a] $Cu(OTf)_2$ was combined with hypervalent iodine(III) compounds **26** to provide arylated indoles **20** or **24** with two kinds of site-selectivities, depending on the nature of the protecting groups on the indole nitrogen (Scheme 17).

[58] (a) R. Weiss, J. Seubert, *Angew. Chem. Int. Ed.* **1994**, *33*, 891–893; (b) V. V. Zhdankin, A. Y. Koposov, N. V. Yashin, *Tetrahedron Lett.* **2002**, *43*, 5735–5737; (c) M. Ochiai, T. Suefuji,K. Miyamoto, M. Shiro, *Chem. Commun.* **2003**, 1438–1439.

[59] N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973.

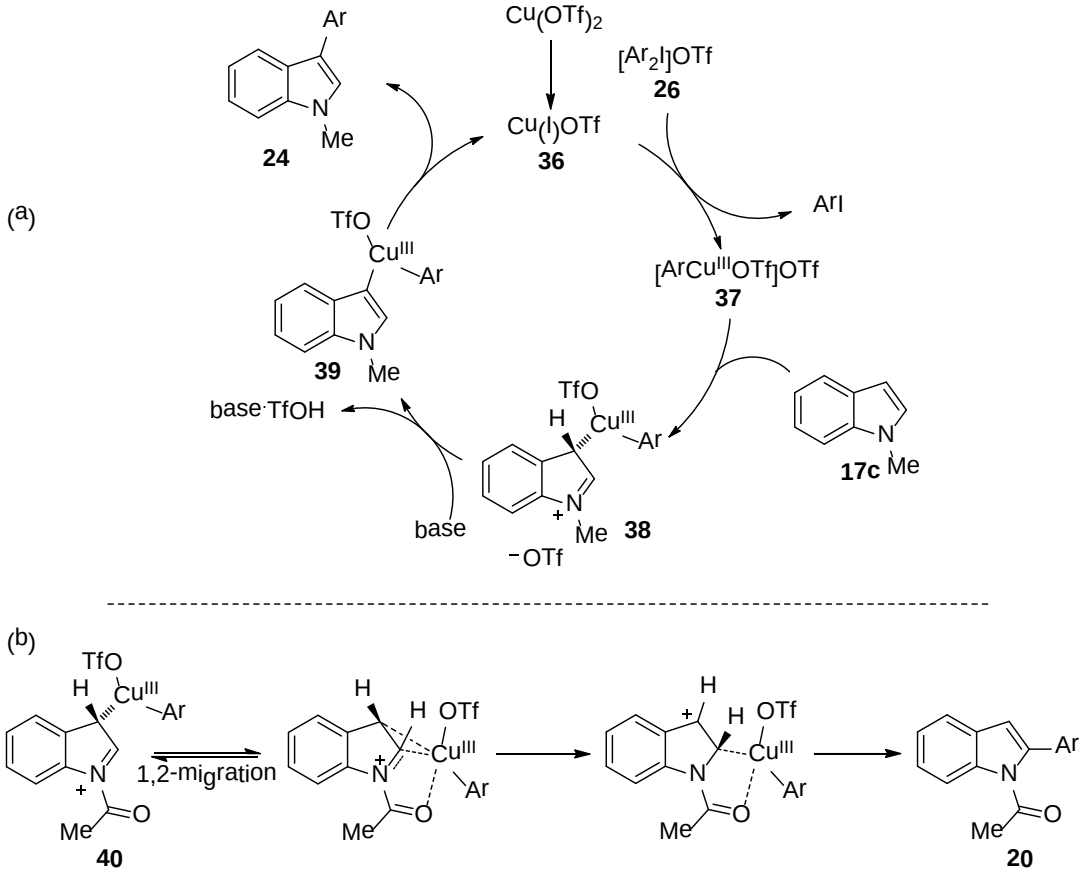
[60] (a) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174. For the selected recent communications, see: (b) N. Gigant, L. Chausset-Boissarie, M.-C. Belhomme, T. Poisson, X. Pannecoucke, I. Gillaizeau, *Org. Lett.* **2013**, *15*, 278–281; (c) M. Prakash, S. Muthusamy, V. Kesavan, *J. Org. Chem.* **2014**, *79*, 7836–7843; (d) C. Liu, W. Zhang, L.-X. Dai, S.-L. You, *Chem. Asian J.* **2014**, *9*, 2113–2118; (e) D. Kumar, M. Pilania, V. Arun, S. Pooniya, *Org. Biomol. Chem.* **2014**, *12*, 6340–6344.

[61] For the recent examples of iron-catalyzed C–H functionalizations with diaryliodonium salts, see: (a) B. R. Vaddula, A. Saha, J. Leazer, R. S. Varma, *Green Chem.* **2012**, *14*, 2133–2136; (b) Z. Shu, W. Ji, X. Wang, Y. Zhou, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 2186–2189.



Scheme 17: Copper-catalyzed direct arylations of indoles **17**.

In terms of the reaction mechanism, the correlation between the protecting group and the regioselectivity is considered as the key factor (Scheme 18).



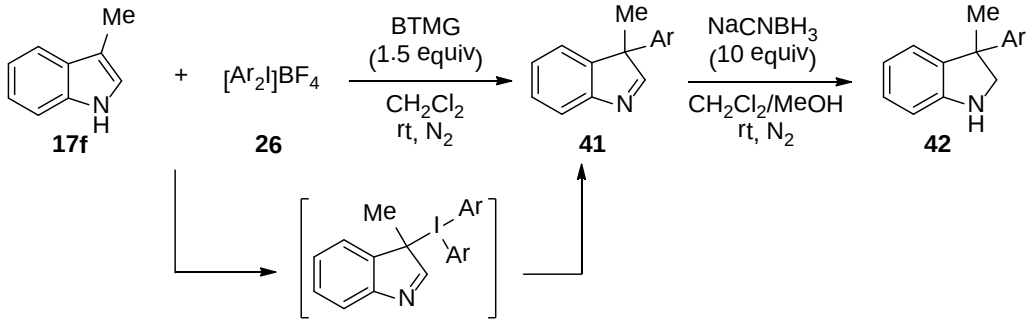
Scheme 18: Proposed catalytic cycles for copper-catalyzed arylations.

As shown in Scheme 18a, in the initial step of reaction the diaryliodonium salt **26** oxidatively adds to $Cu(OTf)_2$. Subsequently, the highly electrophilic aryl-copper(III) species **37** attacks the indole **17c** at the C3 position to form the intermediate **38**. If the indole nitrogen is protected with an alkyl group as in **5d**, the intermediate **38** undergoes rearomatization and then reductive elimination to provide 3-arylindole **24**. On the contrary, an *N*-acetyl group on the nitrogen in **40** interacts with copper(III) species and renders 1,2-migration (Scheme 18b). This reorganization affords the C2-regioisomer **20**.

1.2.2.3 Metal-Free Direct C–H Arylations of (Hetero)Arenes

While the transition metal-catalyzed methods discussed above have found widespread applications, alternatives need to be developed taking into consideration the toxicity and costs of transition metals. In recent years, more efforts focused on metal-free arylations of arenes and heterocycles with hypervalent iodine(III) compounds like diaryliodonium salts, which are also of relevance for the discussion of the mechanism for the metal-catalyzed transformation.

Inspired by the studies of *Barton*,[62] in which the electrophilic pentavalent organobismuth(V) reagent Ph_4BiOTs reacted with 3-methylindole **17f** affording the C3-substituted indolenine **41**, *Baran* employed diaryliodonium salts **26** and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG) for the synthesis of the instable indolenine **41** and the more stable indoline **42** (Scheme 19).[63] It was assumed that the reaction proceeded *via* electrophilic addition of the hypervalent iodine(III) compound **26** to the indole **17f**.

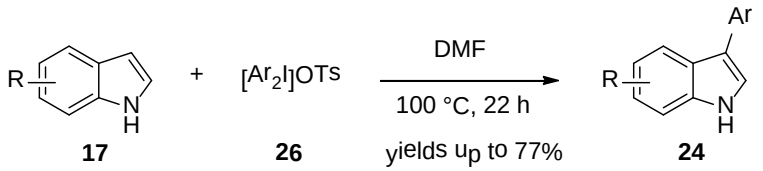


Scheme 19: Arylation of 3-methylindole (**17f**) with $[Ar_2I]BF_4$ (**26**) furnishing indolenine **41**.

In 2011, an efficient regioselective direct C3-arylation of indoles **17** in the absence of any transition metal and base was reported by *Ackermann* (Scheme 20).[64] It was observed that the counteranions of λ^3-iodanes had a remarkable influence on the arylation, with tosylate **26** providing the best results. Notably, competition experiments demonstrated that the more electron-deficient aryl groups in unsymmetrical diaryliodonium salts were preferentially transferred to the indole substrate,[65] and the more electron-rich indoles were predominantly

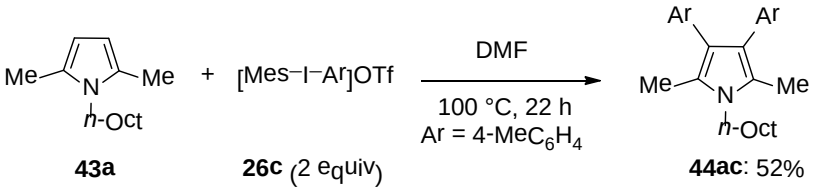
[62] D. H. R. Barton, J.-P. Finet, C. Giannotti, F. Halley, *J. Chem. Soc., Perkin Trans. 1* **1987**, 241–245.
[63] K. Eastman, P. S. Baran, *Tetrahedron* **2009**, *65*, 3149–3154.
[64] L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente, R. Sandmann, *Org. Lett.* **2011**, *13*, 2358–2360.
[65] J. Malmgren, S. Santoro, N. Jalalian, F. Himo, B. Olofsson, *Chem. Eur. J.* **2013**, *19*, 10334–10342.

arylated.



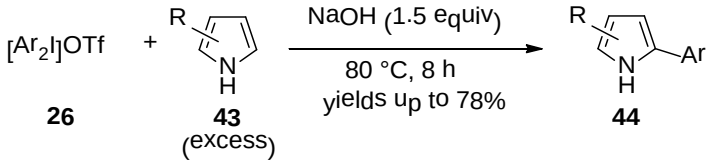
Scheme 20: Direct C3-arylation of indoles **5** as reported by *Ackermann*.

In addition to the indole **17**, the pyrrole **43a** was also a viable substrate under this metal-free condition, delivering the diarylated product **44ac** (Scheme 21).



Scheme 21: Direct arylation of pyrrole **43a**.

Later, *Yu* published a base-mediated C2-arylation of pyrroles **43**, in which an excess of pyrrole was required (Scheme 22).[66] The positive radical trapping tests indicated that the mechanism of the arylation involved the participation of an aryl radical.

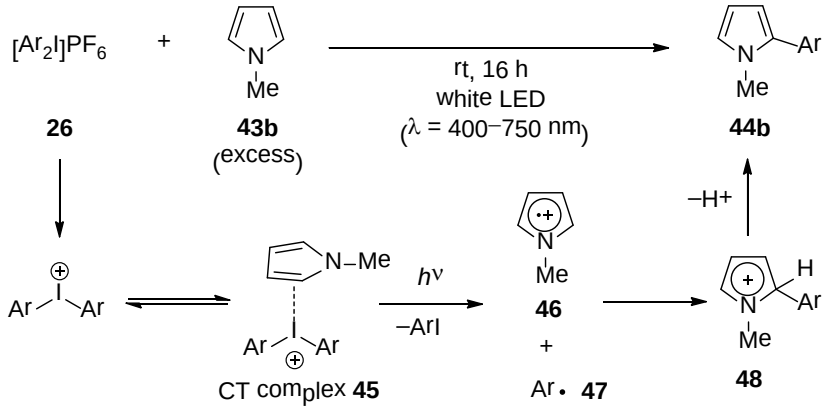


Scheme 22: Base-mediated arylations of pyrroles **43** with diaryliodonium triflates **26**.

Moreover, *Chatani* disclosed that the arylation of pyrroles **43b** can take place even at ambient temperature, when the reaction was irradiated by visible light from a white light-emitting diode (LED) (Scheme 23).[67,68] Basing on the UV-Vis spectroscopic analysis of the reaction mixture, *Chatani* proposed that a charge-transfer (CT) complex **45** was *in situ* generated. Under the LED irradiation, the CT complex **45** is activated to provide the pyrrole radical cation **46** and the aryl radical **47**, both of which are subsequently recombined to afford the

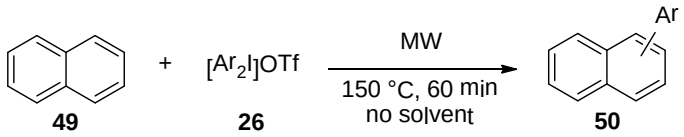
[66] J. Wen, R.-Y. Zhang, S.-Y. Chen, J. Zhang, X.-Q. Yu, *J. Org. Chem.* **2012**, *77*, 766–771.
[67] M. Tobisu, T. Furukawa, N. Chatani, *Chem. Lett.* **2013**, *42*, 1203–1205.
[68] For selected recent communications on visible light-mediated arylations of (hetero)arenes, see: (a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569; (b) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958–2961; (c) S. R. Neufeldt, M. S. Sanford, *Adv. Synth. Cat.* **2012**, *354*, 3517–3522; (d) Y.-X. Liu, D. Xue, J.-D. Wang, C.-J. Zhao, Q.-Z. Zou, C. Wang, J. Xiao, *Synlett* **2013**, *24*, 507–513.

cationic intermediate **48**. The final deprotonation led to the product **44b**.



Scheme 23: Visible light-mediated direct arylations of pyrroles **43b**.

Besides, *Rodríguez* developed a microwave-assisted base- and metal-free C–H bond arylation of such inactivated arenes as naphthalene (**49**) (Scheme 24).[69a] In terms of site-selectivity, *α*-arylated naphthalene **50** was found to be the major product. Moreover, based on the fact that the addition of a radical scavenger TEMPO inhibited the reaction entirely, a radical mechanism was proposed.



Scheme 24: Base- and metal-free C–H arylation of naphthalene (**49**).

1.2.2.4 Mechanisms for Metal-Free Arylations with Diaryliodonium Salts

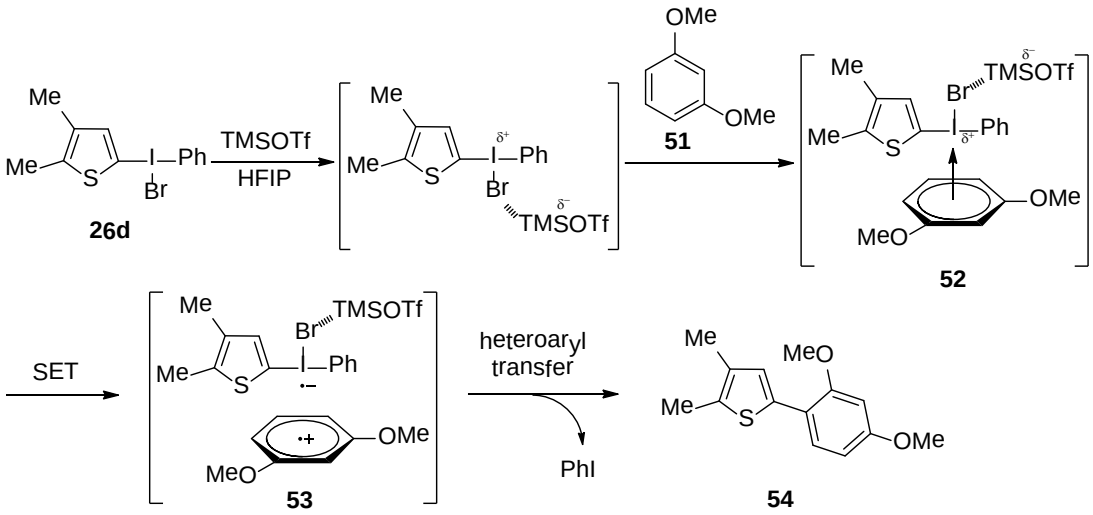
Two kinds of reaction pathways *via* radical or ionic mechanisms could be envisioned for metal-free arylations of (hetero)arenes with diaryliodonium salts.

Investigating the TMSOTf-promoted oxidative coupling of electron-rich arene **51** with phenylthienyliodonium bromide (**26d**) (Scheme 25),[70] *Kita* has found hexafluoroisopropanol

[69] (a) S. Castro, J. J. Fernández, R. Vicente, F. J. Fañanás, F. Rodríguez, *Chem. Commun.* **2012**, *48*, 9089–9091. For the transition metal-free direct C–H functionalization of quinones and naphthoquinones with diaryliodonium salts, see: (b) D.Wang, B. Ge, L. Li, J. Shan, Y. Ding, *J. Org. Chem*. **2014**, *79*, 8607–8613**.**

[70] (a) T. Dohi, M. Ito, K. Morimoto, M. Iwata, Y. Kita, *Angew. Chem. Int. Ed.* **2008**, *47*, 1301–1304; (b) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto, T. Dohi, *J. Am. Chem. Soc.* **2009**, *131*, 1668–1669; (c) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Angew. Chem. Int. Ed.* **2010**, *49*, 3334–3337; (d) K. Morimoto, N. Yamaoka, C. Ogawa, T. Nakae, H. Fujioka, T. Dohi, Y. Kita, *Org. Lett.* **2010**, *12*, 3804–3807.

(HFIP) as the solvent to be crucial for the reaction, because of its good stabilizing properties. Moreover, the radical species formed from electron-rich arene **51** was detected by ESR spectroscopy.[70c] Hence, the reaction presumably proceeded *via* a radical mechanism involving a step of single-electron-transfer (SET)[71] from the charge transfer complex **52** affording the radical anion/radical cation pair **53**. Then, the electron-rich heteroaryl group was transferred from the radical anion moiety **53** to its radical cation fragment furnishing the product **54**.

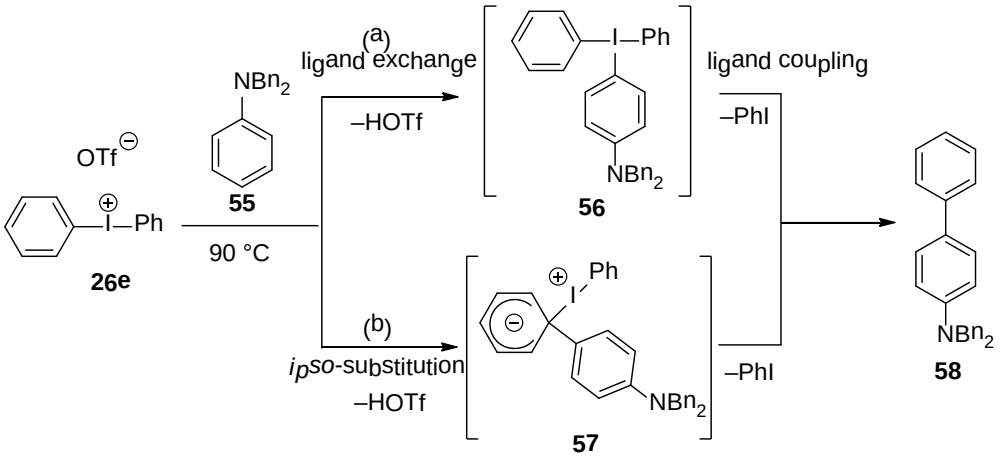


Scheme 25: SET reaction pathway for λ^3-iodine(III) mediated oxidative couplings of arenes.

On the contrary, *Gaunt* regarded the arylation of electron-rich arenes as a Friedel-Crafts-type reaction.[72] Two possible pathways may render the biaryl formation (Scheme 26). An electron-rich arene **55** might attack the electrophilic diphenyliodonium salt **26e** to form the trivalent iodine **56** *via* ligand exchange, which is unstable and quickly decomposes to the biaryl **58** *via* ligand coupling (pathway a), or through *ipso*-substitution on aniline **55** with a phenyl group from the diphenyliodonium salt **26e** (pathway b).

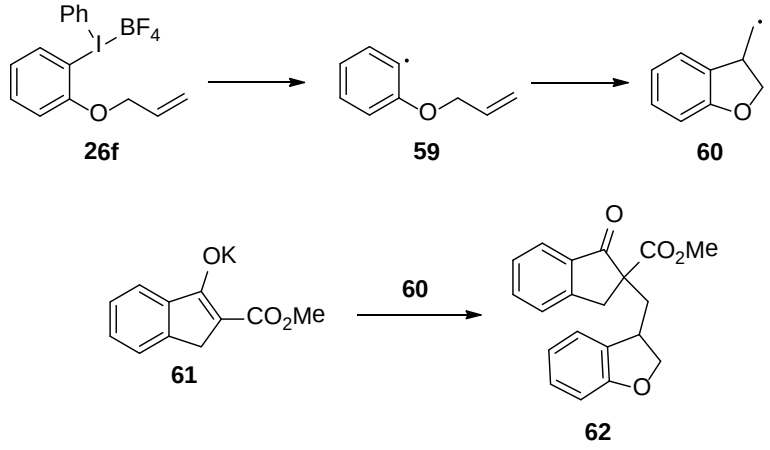
[71] E. C. Ashby, *Acc. Chem. Res.* **1988**, *21*, 414–421.

[72] (a) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 458–462; (b) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 463–466.



Scheme 26: Ionic Friedel-Crafts-type mechanism.

To gain insight into the mechanism for mono- and diarylations of 1,3-dicarbonyl compounds with diaryliodonium salts,[73] *Ochiai* examined an arylation of *β*-keto ester enolates **61** with [(*o*-allyloxy)phenyl](phenyl)iodonium tetrafluoroborate (**26f**).[74] If a radical mechanism was operative in this reaction, the hypervalent iodine(III) compound **26f** would easily decompose to (*o*-allyloxy)phenyl radical (**59**). The latter should undergo an intramolecular radical cyclization affording (2,3-dihydrobenzofuran-3-yl)methyl radical (**60**), which further reacts with *β*-ketoester enolate **61** furnishing the product **62** (Scheme 27).

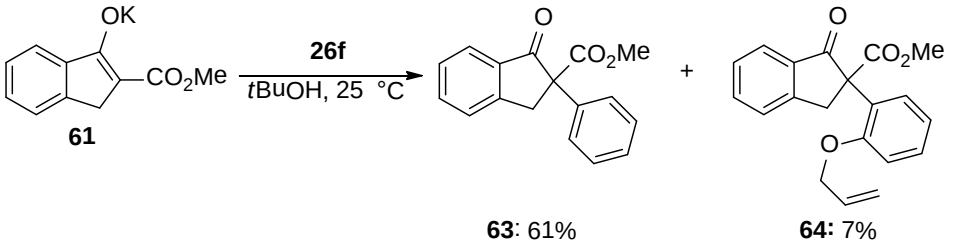


Scheme 27: Potential cyclization of substrate **57**.

However, as shown in Scheme 28, this reaction afforded only α-phenylated and *α*-(*o*-allyloxy)phenylated products **63** and **64**, respectively, in a ratio of 9:1, and no evidence for the formation of 3-substituted dihydrobenzofuran derivative **62** was obtained. Hence, an

[73] F. M. Beringer, P. S. Forgione, M. D. Yudis, *Tetrahedron* **1960**, *8*, 49–63.
[74] (a) D.-W. Chen, M. Ochiai, *J. Org. Chem.* **1999**, *64*, 6804–6814; (b) M. Ochiai, Y. Kitagawa, M. Toyonari, *ARKIVOC* **2003**, *vi*, 43–48.

ionic mechanism is more likely to be involved in this arylation reaction.



Scheme 28: Arylation of 2-(methoxycarbonyl)-1-indanone.

It should be noted that the exact mechanism for any given example depends not only on the nature of the hypervalent iodine(III) compounds, but also on the substrate, solvent, additive and reaction temperature.[75]

1.3 Transition Metal-Catalyzed Synthesis of Aryl Pyrroloindolines

Pyrroloindoline represents an important scaffold of many nitrogen-containing alkaloids.[76] Its tricyclic moiety delivers a diverse range of possibilities for post-synthetic modifications, affording natural products with compelling biological activities, such as asperazine,[77a] naseseazine A[77b] and gliocladine C[c] (Figure 5).

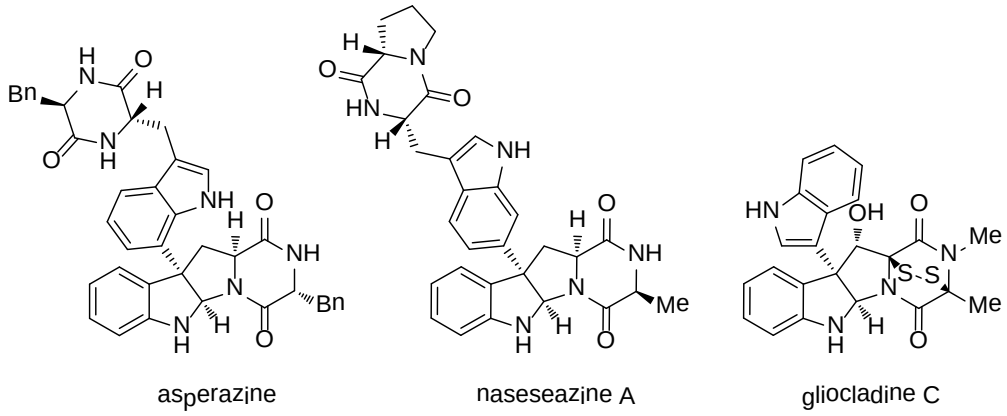


Figure 5: Representative naturally occurring pyrroloindolines.

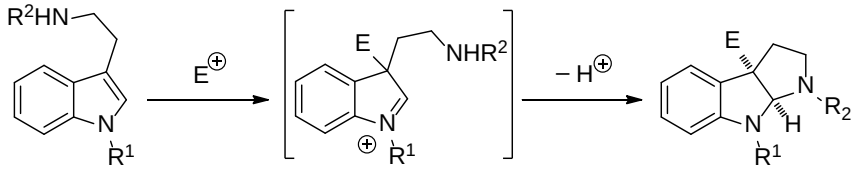
As a result, a variety of new synthetic methods were investigated to synthesize the key

[75] A. Sreenithya, R. B. Sunoj, *Org. Lett.* **2014**, *16*, 6224–6227.

[76] U. Anthoni, C. Christophersen, P. H. Nielsen, *Naturally Occurring Cyclotryptophans and Cyclotryptamines*, in *Alkaloids: Chemical & Biological Perspectives*; S. W. Pelletier, Ed.; Pergamon: Oxford, **1999**, vol. 13, pp. 163 ff.

[77] (a) M. Varoglu, T. H. Corbett, F. A. Valeriote, P. Crews, *J. Org. Chem.* **1997**, *62*, 7078–7079; (b) R. Raju, A. M. Piggott, M. Conte, W. G. L. Aalbersberg, K. Feussner, R. J. Capon, *Org. Lett.* **2009**, *11*, 3862–3865; (c) J.-Y. Dong, H.-P. He, Y.-M. Shen, K.-Q. Zhang, *J. Nat. Prod.* **2005**, *68*, 1510–1513.

pyrroloindoline core.[78] Among them, the strategy, in which an electrophile first reacts with a tryptophan or a tryptamine through S_EAr attack followed by a subsequent iminium trapping/cyclization, has been emerging as a convenient and versatile method (Scheme 29).



Scheme 29: Electrophilic cyclization to pyrroloindoline.

Up to now, various electrophiles were recognized as appropriate reaction partners. Among them are diazoacetate for cyclopropanation/ring-opening/iminium cyclization reactions,[79] selectfluor for fluorocyclizations,[80] NBS or Br_2 for bromination-cyclizations,[81] aniline with NCS as oxidant, or *o*-iodoaniline with NIS as oxidant for electrophilic amination-cyclizations, [82] *N*-phenylselenophthalimide (*N*-PSP) for selenocyclizations, [83] dimethyldioxirane (DMDO) for cyclizations *via* epoxidation/nucleophilic ring opening,[84] and *α*,*β*-unsaturated ketones for Michael addition-cyclizations (MIRC reactions).[85]

[78] For selected reviews on this topic, see: (a) D. Crich, A. Banerjee, *Acc. Chem. Res*. **2007**, *40*, 151–161; (b) A. Steven, L. E. Overman, *Angew. Chem. Int. Ed*. **2007**, *46*, 5488–5508; (c) J. Kim, M. Movassaghi, *Chem. Soc. Rev*. **2009**, *38*, 3035–3050; (d) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem. Eur. J.* **2011**, *17*, 1388–1408; (e) L. M. Repka, S. E. Reisman, *J. Org. Chem.* **2013**, *78*, 12314–12320.

[79] (a) H. Song, J. Yang, W. Chen, Y. Qin, *Org. Lett.* **2006**, *8*, 6011–6014; (b) B. He, H. Song, Y. Du, Y. Qin, *J. Org. Chem.* **2009**, *74*, 298–304; (c) D. Zhang, H. Song, Y. Qin, *Acc. Chem. Res.* **2011**, *44*, 447–457.

[80] N. Shibata, T. Tarui, Y. Doi, K. L. Kirk, *Angew. Chem. Int. Ed.* **2001**, *40*, 4461–4463.

[81] (a) C. S. López, C. Pérez-Balado, P. Rodríguez-Graña, A. R. De Lera, *Org. Lett.* **2008**, *10*, 77–80; (b) P. Ventosa-Andrés, J. A. González-Vera, Á. M. Valdivielso, M. T. García-López, R. Herranz, *Bioorg. Med. Chem.* **2008**, *16*, 9313–9322; (c) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378.

[82] (a) T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887; (b) T. Newhouse, C. A. Lewis, K. J. Eastman, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137.

[83] (a) S. P. Marsden,K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.* **1994**, *116*, 11143–11144; (b) M. K. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963; (c) D. Crich, X. Huang, *J. Org. Chem.* **1999**, *64*, 7218–7223; (d) S. V. Ley, E. Cleator, P. R. Hewitt, *Org. Biomol. Chem.* **2003**, *1*, 3492–3494; (e) P. R. Hewitt, E. Cleator, S. V. Ley, *Org. Biomol. Chem.* **2004**, *2*, 2415–2417.

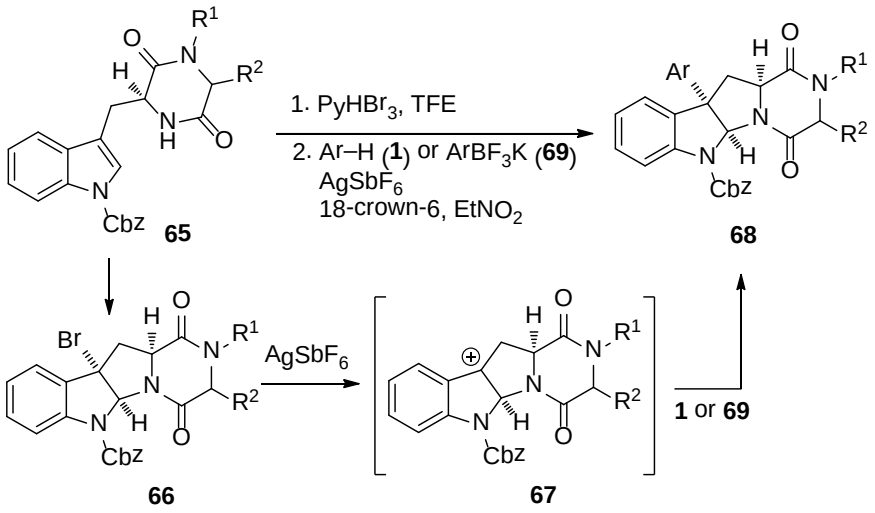
[84] T. M. Kamenecka; S. J. Danishefsky, *Angew. Chem. Int. Ed.* **1998**, *37*, 2995–2998.

[85] (a) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482–5487; (b) Q. Cai, C. Liu, X.-W. Liang, S.-L. You, *Org. Lett.* **2012**, *14*, 4588–4590.

1.3.1 Synthesis of C3-Arylated Pyrroloindolines

Despite the great progress in the oxidative as well as in the organo- or transitionmetal-catalyzed cyclization, the synthesis of C3-arylpyrroloindolines has remained a challenging work until recently.

In 2011, *Movassaghi* reported a two-step synthesis of C3-arylated pyrroloindoline **68** from the corresponding tryptophan derivative **65**, in which a bromocyclization affording **66** occurred first, followed by a electrophilic substitution with an electron-rich arene **1** or a potassium aryltrifluoroborate (**69**) on the carbocation **67** (Scheme 30).[86]

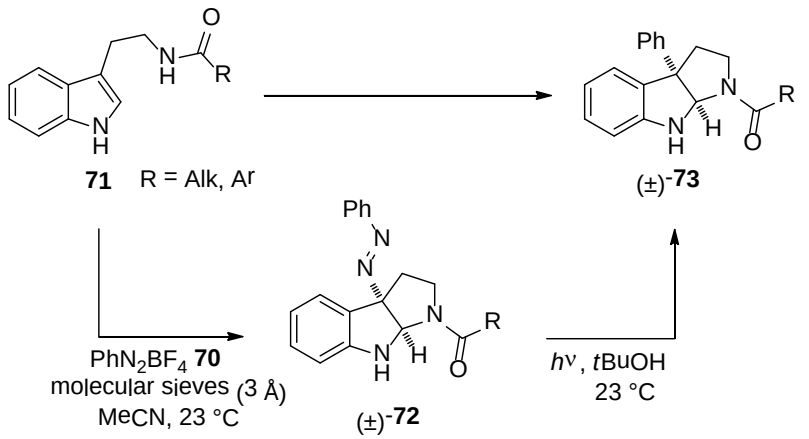


Scheme 30: Two steps-approach to C3-arylated pyrroloindolines **68**.

More recently, the aryldiazonium salt **70** was utilized to enable the synthesis of the racemic C3-diazenated pyrroloindoline (±)-**72**. This unsymmetrical azo-intermediate (±)-**72** was then irradiated to afford the racemic C3-arylpyrroloindoline (±)-**73** (Scheme 31).[87]

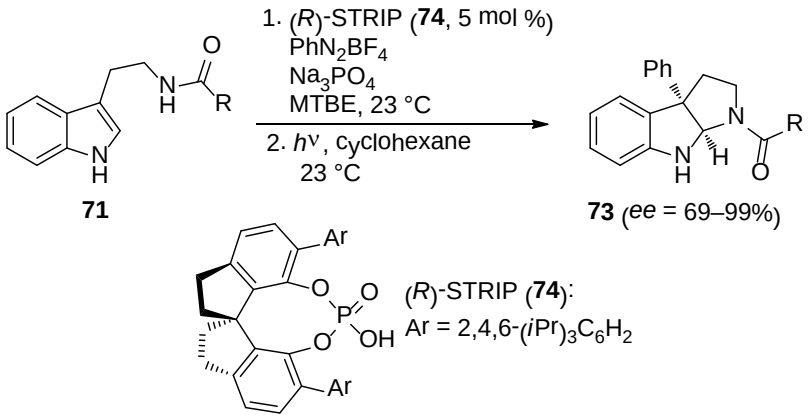
[86] (a) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943; (b) N. Boyer, M. Movassaghi, *Chem. Sci.* **2012**, *3*, 1798–1803.

[87] D. E. Stephens, O. V. Larionov, *Eur. J. Org. Chem.* **2014**, 3, 662–3670.



Scheme 31: Assembly of C3-arylated pyrroloindoline (±)-**73a** through diazenation and nitrogen extrusion by photoirradiation.

Interestingly, the employment of a catalytic amount of a chiral phosphoric acid, such as (*R*)-STRIP **74**, resulted in a highly enantioselective formation of the C3-diazenated intermediate and the corresponding C3-arylated product **73** with high *ee* values (Scheme 32).[88] This outstanding property was attributed to a chiral anion phase transfer (CAPT), in which the chiral phosphoric acid **74** interacted with the insoluble aryldiazonium compound to form a soluble chiral ion pair.



Scheme 32: Enantioselective synthesis of C3-phenylated pyrroloindolines **73**.

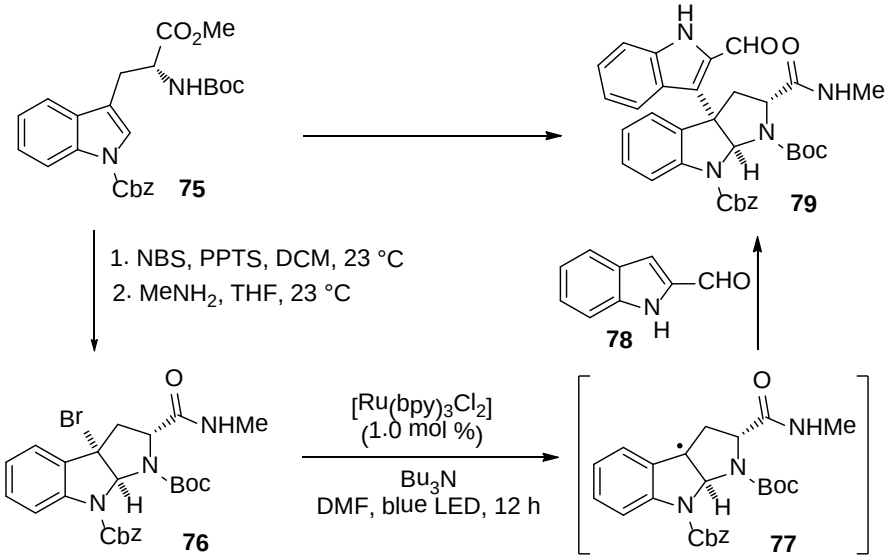
Since *Zen* published a selective and efficient photocatalytic oxidation of sulfides in the presence of a ruthenium photocatalyst in 2003,[89] visible light photoredox catalysis has experienced a renaissance in organic synthesis.[90] This strategy was recently applied to the

[88] H. M. Nelson, S. H. Reisberg, H. P. Shunatona, J. S. Patel, F. D. Toste, *Angew. Chem. Int. Ed.* **2014**, *53*, 5600–5603.

[89] J. M. Zen, S. L. Liou, A. S. Kumar, M. S. Hsia, *Angew. Chem. Int. Ed.* **2003**, *42*, 577–579.

[90] For selected reviews on visible light photoredox catalysis, see: (a) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; (b) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838; (c) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387–2403; (d) D.

[Ru(bpy)$_3$Cl$_2$]-catalyzed reductive debromination of C3-bromopyrroloindolines **76** under irradiation with a fluorescent bulb. In the meantime, a pyrroloindoline radical **77** was first produced and then reacted with indole-2-carboxaldehyde (**78**) to form C3-(3-indolyl)pyrroloindoline **79** (Scheme 33).[91] Employing this key step, the (+)-gliocladin can subsequently be synthesized in moderate yield.



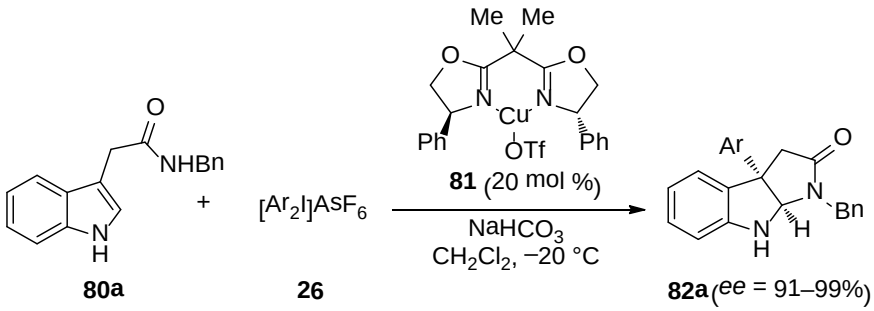
Scheme 33: Visible light-mediated C3-heteroarylation.

Although the above mentioned three procedures were concise and promising, the low yields after two separated steps prompted chemists to seek an alternative direct reaction. In 2012, *MacMillan* reported on a copper-catalyzed arylation-cyclization cascade of indolylacetamide **80a** with diaryliodonium salts **26** in the presence of a tailor-made chiral copper-ligand complex **81**, affording pyrroloindolones **82** with high *ee* values (Scheme 34).[92] Compounds **82a** can simply be converted to the desired pyrroloindoline through a reduction with LiAlH$_4$.

P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 2–12.

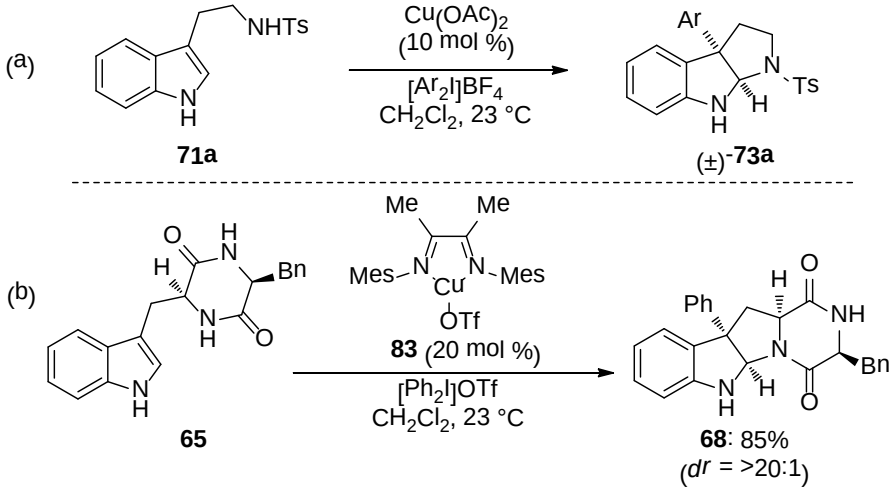
[91] (a) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757; (b) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2011**, *50*, 9655–9659.

[92] S. Zhu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 10815–10818.



Scheme 34: Copper-catalyzed enantioselective arylation-cyclization cascade.

At the same time, a similar copper-catalyzed reaction of tryptamine **71a** was developed by *Reisman*, delivering a racemic C3-arylated pyrroloindoline (±)-**73a** (Scheme 35a).[93a] Unfortunately, employing the chiral copper catalyst **81** used in *MacMillan*'s reaction, no further improvement of enantioselectivity was observed. Alternatively, enantioselectivity could be achieved by transmission of the stereochemical information from the α-carbon of enantiomerically pure starting material to the newly formed quaternary center. Thus, the arylation-cyclization of diketopiperazine **65** in the presence of the copper complex **83** provided the diastereomer **68** with a high *dr* value, which were subsequently employed to synthesize (+)-naseseazines A and B (Scheme 35b).[93b]



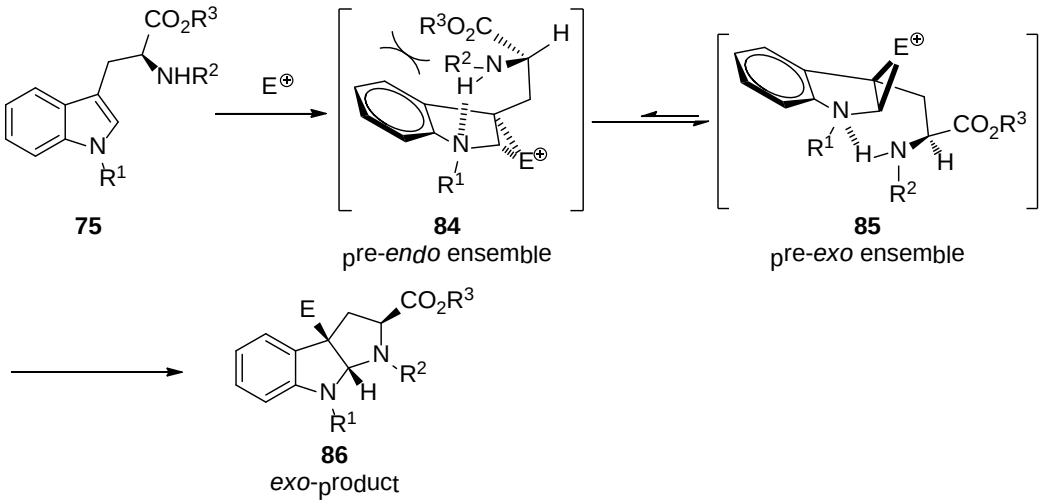
Scheme 35: Copper-catalyzed direct construction of C3-arylated pyrroloindolines.

[93] (a) M. E. Kieffer, K. V. Chuang, S. E. Reisman, *Chem. Sci.* **2012**, *3*, 3170–3174; (b) M. E. Kieffer, K. V. Chuang, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 5557–5560.

1.3.2 Stereoselectivity of the Pyrroloindoline Synthesis

The problem of stereoselectivity constantly accompanies the synthesis of pyrroloindolines. For the reaction of substrates without any chiral center such as tryptamine **71**, the enantioselectivity could be introduced through the utilization of a chiral organocatalyst (Scheme 32) or a chiral metal-ligand complex (Scheme 34). As to (L)-tryptophan derivative **75** bearing an innate chiral center, the *exo* configuration is remarkably favored compared to the *endo*-form, when the electrophile and the substituent on the *N*- or *C*-terminus are sterically demanding.[82b]

In the electrophilic addition/cyclization reaction sequence, two kinds of intermediates could be imagined (Scheme 36). The pre-*endo* ensemble **84** possesses a steric clash between the carboxylate functionality and the indole nuclei, leading to a kinetic instability. On the contrary, the pre-*exo* ensemble 8**5** is free of this kind of steric restraint and smoothly affords the corresponding *exo*-diastereomer **86**.



Scheme 36: Proposed rationalization of the high *exo*-diasteroselectivity.

1.4 Late-Stage Diversification of Peptides by Direct C–H Arylations

Over decades, peptides have found a broad spectrum of applications in pharmaceutical industry and asymmetric catalysis. Compared to small molecular drugs, peptides have gradually gained more market share owing to their more diversity, selectivity and low toxicity.[94] Moreover, peptides as competitive chiral building blocks, chiral ligands or chiral catalysts have been employed in the total synthesis and ligand elaboration.[95]

Within the exploration of methods enabling a rapid derivatization of peptides to a panel of closely related analogues and streamline the synthesis, late-stage modifications have become a useful tool.[96] Chemo- and site-selective chemical transformations of peptides have so far mostly relied on prefunctionalized unnatural amino acids embedded within the peptides in advance. These strategies can be defined as "Tag-and-Modify" approaches (Scheme 37).[97] After the preparation of Tag-containing peptides, the corresponding modification can be site-selectively performed *via* palladium-catalyzed Suzuki-Miyaura cross-coupling reactions (Scheme 37a, b),[98] copper-catalyzed azide-alkyne [3+2] Huisgen-cycloadditions (Scheme 37c, d),[99] or ruthenium-catalyzed olefin metathesis (Scheme 37e).[100]

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[94] (a) F. Albericio, H. G. Kruger, *Future Med. Chem.* **2012**, *4*, 1527–1531; (b) A. A. Kaspar, J. M. Reichert, *Drug Discovery Today* **2013**, *18*, 807–817; (c) D. J. Craik, D. P. Fairlie, S. Liras, D. Price, *Chem. Biol. Drug Des.* **2013**, *81*, 136–147.

[95] (a) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; (b) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036–12041.

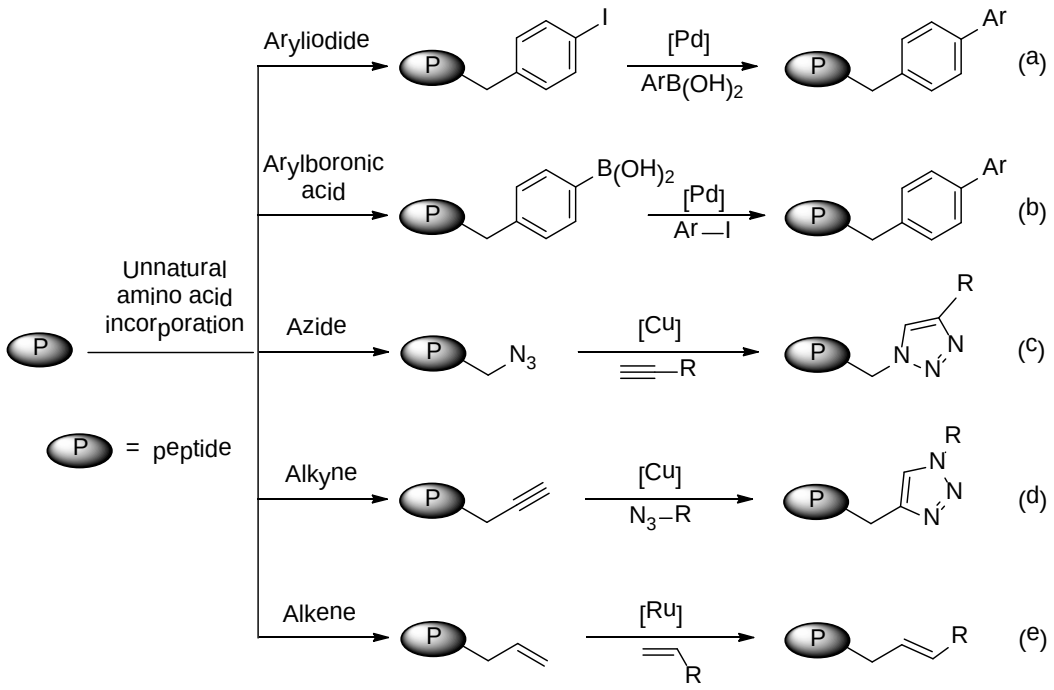
[96] (a) J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369–375; (b) A. F. M. Noisier, M. A. Brimble, *Chem. Rev.* **2014**, *114*, 8775–8806.

[97] J. M. Chalker, G. J. L. Bernardes, B. G. Davis, *Acc. Chem. Res.* **2011**, 44, 730–741.

[98] (a) E. Brustad, M. L. Bushey, J. W. Lee, D. Groff, W. Liu, P. G. Schultz, *Angew. Chem. Int. Ed.* **2008**, *47*, 8220–8223; (b) Z. Gao, V. Gouverneur, B. G. Davis, *J. Am. Chem. Soc.* **2013**, *135*, 13612–13615.

[99] (a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; (b) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193; (c) S. I. van Kasteren, H. B. Kramer, H. H. Jensen, S. J. Campbell, J. Kirkpatrick, N. J. Oldham, D. C. Anthony, B. G. Davis, *Nature* **2007**, *446*, 105–1109.

[100] Y. A. Lin, J. M. Chalker, B. G. Davis, *ChemBioChem* **2009**, *10*, 959–969.



Scheme 37: The "Tag-and-Modify" approach to peptide modification.

In addition, an alternative strategy could be adopted by exploiting ubiquitous C(sp^2)–H bonds as a latent functional group and an ideal point of diversification.[101]

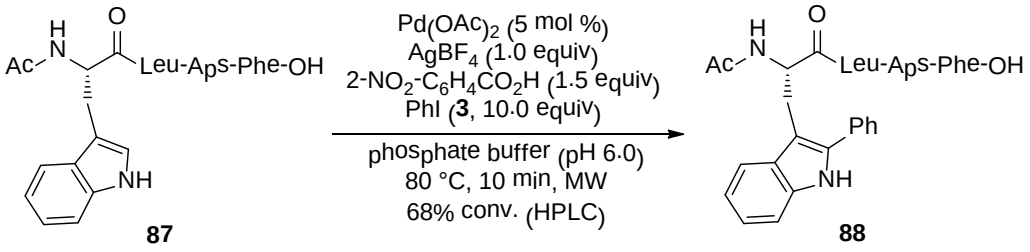
Among native α-amino acids, tryptophan possesses a heteroaromatic side chain, which is a favorable fluorescent probe with a relatively high fluorescence quantum yield.[102a] Because of its large dipole moment of the excited state, the spectroscopic properties are highly sensitive to the specific conditions.[102b] By changing its surroundings, the fluorescence quantum yield and emission maximum vary significantly. Furthermore, tryptophan is found in relatively low abundance in proteins or peptides. These properties render tryptophan widely exploited for protein quantifications and explorations of protein dynamics, folding, binding and protein-protein interactions.[103] Hence, these appealing advantages of tryptophan have prompted chemists to seek general and site-selective chemical methods to modify and intensify the tryptophan's fluorescence.

Based on a number of transition metal-catalyzed direct C–H arylations of simple indoles with excellent regioselectivities (see Chapter 1.2), similar strategies were applied to the

[101] J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed*. **2012**, *51*, 8960–9009.
[102] (a) J. A. Ross, D. M. Jameson, *Photochem. Photobiol. Sci.* **2008**, *7*, 1301–1312; (b) D. W. Pierce, S. G. Boxer, *Biophys J.* **1995**, *68*, 1583–1591.
[103] R. W. Sinkeldam, N. J. Greco, Y. Tor, *Chem. Rev.* **2010**, *110*, 2579–2619.

tryptophan-containing peptides to provide biaryl moieties.

Following *Larrosa*'s reaction conditions, *Lavilla* developed a microwave-assisted direct C–H arylation of tryptophan-containing peptides **87** with a 10-fold excess of aryl iodide **3** in a phosphate buffer (pH = 6.0) at 80 °C, which afforded the arylated peptide **88** with 68% conversion (Scheme 38).[104a] This approach displayed a high regioselectivity and good tolerance to other unprotected amino acid moieties, such as phenylalanine, tyrosine, arginine, histidine, lysine, serine, glutamine. The position of the tryptophan within the peptide sequence has no impact on the efficiency of this chemical transformation. More importantly, chiral HPLC studies indicated that no racemization occurred during the reaction, which makes the arylation reaction more attractive. Later, *Lavilla* found an alternative method to obtain modified peptides through the initial arylation of Fmoc-protected tryptophan and subsequent solid phase-supported peptide synthesis.[104b]



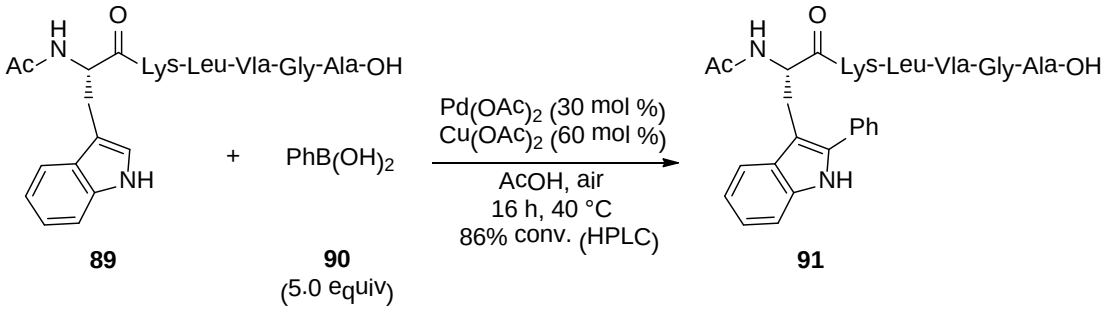
Scheme 38: Palladium-catalyzed arylation of tryptophan-containing peptides **87** with aryl iodides **3**.

Phenylboronic acid (**90**) could be an alternative arylating reagent to modify the tryptophan-containing hexapeptide **89** in the presence of $Cu(OAc)_2$ and O_2 as oxidants, delivering the product with 86% conversion, albeit with high loading of palladium catalyst and copper oxidant (Scheme 39).[105] Interestingly, *Fairlamb* observed and verified that Palladium^0 nanoparticles (PdNPs) were formed *in situ* in the early stages of the reaction, and the pre-synthesized encapsulated PdNPs catalyzed the transformation of tryptophan as well. Therefore, *Fairlamb* assumed heterogeneous catalysis with a palladium(0)/palladium(II) catalytic cycle for the reactions.The active palladium(0) species is generated by the reduction

[104] (a) J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124–1127; (b) S. Preciado, L. Mendive-Tapia, F. Albericio, R. Lavilla, *J. Org. Chem.* **2013**, *78*, 8129–8135.

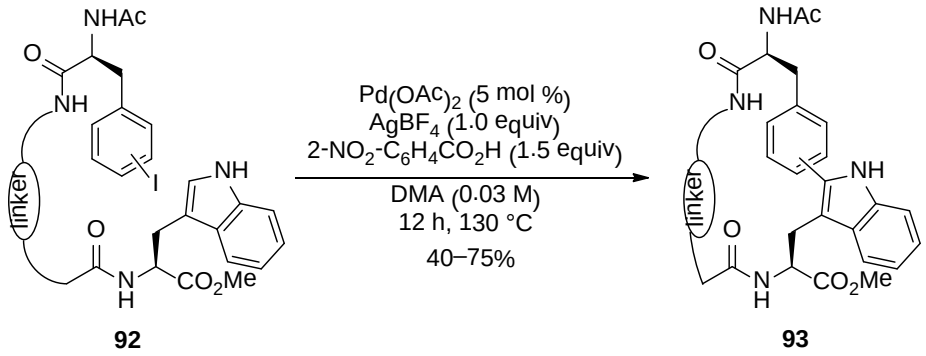
[105] T. J. Williams, A. J. Reay, A. C. Whitwood, I. J. S. Fairlamb, *Chem. Commun.* **2014**, *50*, 3052–3054.

of the precatalyst $Pd(OAc)_2$. The palladium(0)/palladium(II) reduction potential can be lowered by the coordination of two acetamide moieties within peptides to $Pd(OAc)_2$.



Scheme 39: Palladium-catalyzed arylation of peptide **89** with phenylboronic acid (**90**).

Despite the increasing pharmaceutical values of peptides, there are still some negative factors limiting their advance, such as poor pharmacokinetic properties. One possible method to overcome this hurdle is to generate more stable macrocyclic peptides mimicking the structure of peptides.[106] For this purpose, *James* synthesized a series of linear peptides **92** containing a tryptophan at the *C*-terminus and a *para*-/*meta*-iodinated phenylalanine at the *N*-terminus. The subsequent palladium-catalyzed C–H bond arylation of tryptophans accomplished the intramolecular cyclization, providing 15- to 25-membered peptide rings **93** (Scheme 40).[107]



Scheme 40: Peptide macrocyclization *via* palladium-catalyzed C–H arylations of tryptophans.

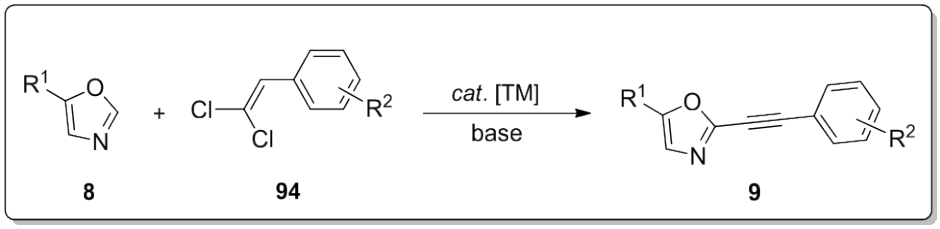
[106] E. M. Driggers, S. P. Hale, J. J. Lee, N. K. Terrett, *Nat. Rev. Drug Discovery* **2008**, *7*, 608–624.

[107] H. Dong, C. Limberakis, S. Liras, S. Price, K. James, *Chem. Commun.* **2012**, *48*, 11644–11646.

2 Objectives

Due to the importance of the highly functionalized *N*-heterocycles, the development of sustainable strategies for their syntheses have sustained required. Ongoing researches by the group of *Prof. Ackermann* and others showed that the transition metal-catalyzed C–H functionalization is a powerful synthetic tool to meet this challenge. Besides, metal-free methodologies have also attracted high attentions, with which the employment of toxic transition metals could be avoided. The works presented within this thesis are focused on the efficient synthesis of heterocyclic molecules in the presence or absence of the transition metals.

In light of the demand for a convenient synthesis of unsymmetrical acetylenes **9**, several successful preparations were recently achieved by *Piguel via* copper-catalyzed direct alkynylations of heteroarenes with bromoacetylenes **6**[22] or *gem*-dibromoalkenes **10**. The utilization of more economical but less reactive *gem*-dichloroalkenes **94**, however, remained a challenging work. On the basis of optimized reaction conditions by *Kornhaaß,*[108] which involved a palladium catalyst combined with a DPE-Phos ligand, the first project presented within this thesis was the extension of the scope of oxazoles **8** and *gem*-dichloroalkenes **94** (Scheme 41).

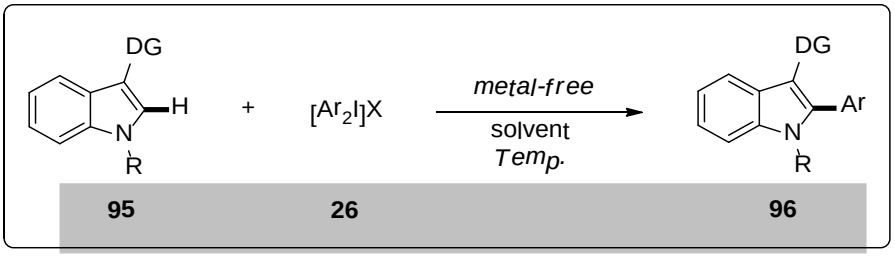


Scheme 41: Palladium-catalyzed alkynylation of oxazoles **8** with *gem*-dichloroalkenes **94**.

The C2-arylated indole is a ubiquitous moiety in natural products and synthetic molecules.[29] Besides the common well-known traditional methods,[32] the recently developed methodologies employ C–H arylations in the presence of transition metal catalysts, such as palladium or copper. On the basis of the ongoing research directed towards the convenient and efficient C–H functionalization of (hetero)arenes, a metal-free direct arylation of indoles

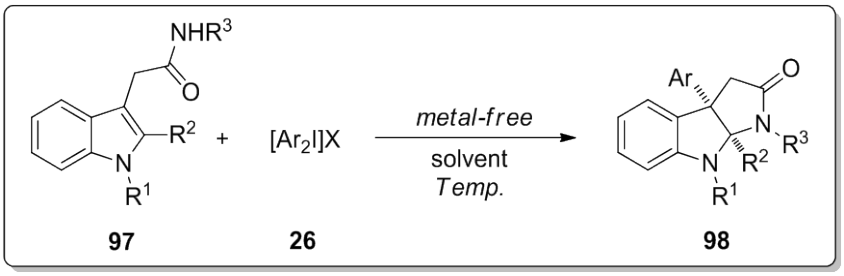
[108] C. Kornhaaß, *Dissertation*, Universität Göttingen, **2014**.

with symmetrical diaryliodonium tosylates **26**, occurring regioselectively at the C3 position of the indoles **17**, was reported by the group of *Ackermann* (Scheme 20). Thereafter, we were interested in developing direct C2-arylations of indoles **95** with a directing group at the C3-position in the absence of any transition metal catalyst (Scheme 42). Moreover, mechanistic studies should be carried out to gain deeper insight into the working mode of these arylation reactions.



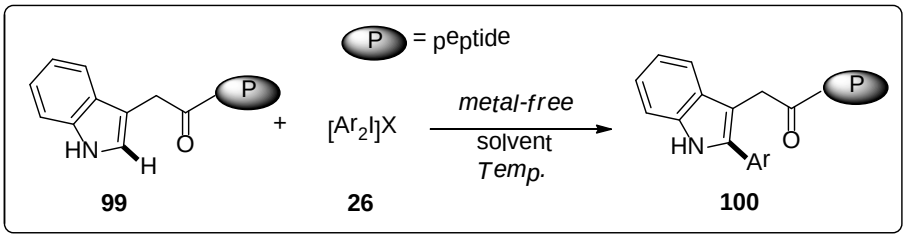
Scheme 42: Metal-free C2-arylation of indoles **95** with hypervalent λ^3-iodanes **26**.

For the arylation-cyclization cascade reaction of tryptamine-derived substrates **97** with diaryliodonium salts **26**, a transition metal catalyst is generally necessary. Taking into account the success in the metal-free C2 arylations of 2-substituted indoles **95**, the metal-free synthesis of C3-arylated pyrroloindolones **98** utilizing the diaryliodonium salts **26** should also be feasible (Scheme 43).



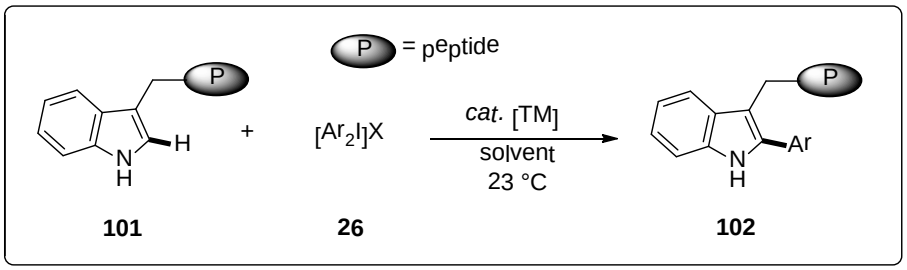
Scheme 43: Metal-free arylation-cyclization cascade reactions.

With regard to the attractive potential of the direct regioselective labeling of bioactive peptides or proteins and the biological understanding as well as the targeted medical imaging, a variety of late-stage functionalizations of peptides or proteins were discovered over last decades.[96–107] Based on the above developed strategy for the metal-free arylation of simple indoles, the more challenging peptide-containing indolylacetamides **99** should be tested (Scheme 44).



Scheme 44: Metal-free late-stage arylation of peptide-containing indolylacetamides **99**.

The amino acid tryptophan is an ideal target for chemical modifications, due to its inherent indole moiety and distinct spectroscopic properties. *Lavilla* and *Fairlamb* successively developed two methods to achieve transition metal-catalyzed arylation of tryptophan-containing peptides. In order to maintain the high reactivities, however, a high amount of the catalyst loading and the arylating agent as well as an elevated reaction temperature were required. Hence, diaryliodonium salts **26** as highly electrophilic arylating reagents should be employed with a purpose to make reactions more efficient and to perform mild late-stage arylations of tryptophan-containing peptides **101** at ambient reaction temperature (Scheme 45).



Scheme 45: Transition metal-catalyzed arylation of tryptophan-containing peptides **101**.

3 Results and Discussion

3.1 Palladium-Catalyzed C–H Alkynylations of Oxazoles

Due to versatile applications of the acetylene moiety in organic chemistry, chemical biology and materials sciences,[109] a variety of powerful and convenient approaches for the synthesis of unsymmetrical acetylenes was developed over the past decades.[110]

Since *Zapata* employed *gem*-dibromoalkenes **10** to synthesize enynes *via* the Stille reactions with 1-propenyltributyltin in the presence of palladium and copper catalysts for the first time,[111] *gem*-dihaloalkenes have been used to accomplish direct alkynylations of unreactive arenes. Meanwhile, because *gem*-dihaloalkenes can readily be synthesized from aldehydes by dihalomethylenations, [112] the present strategy has opened a general and convenient transformation of aldehydes to unsymmetrical alkynes.

While direct alkynylations of oxazoles **8** with bromoacetylenes **6** or *gem*-dibromoalkenes **10** smoothly proceeded in moderate to good yields, the utilization of more economical but less reactive *gem*-dichloroalkenes **94** remains a challenging task. Within the program on streamlining of organic synthesis through sustainable metal-catalyzed direct C–H bond functionalizations, the *gem*-dichloroalkene's **94** reactivity was explored in our group.

After the optimization of reaction conditions by *Kornhaaß*, the desired C2-alkynylated benzoxazole **9aa** was afforded in the presence of $Pd(OAc)_2$, DPEPhos and Li*O*t*Bu* in good yield (Scheme 46). Notably, the catalyst $CuBr{\cdot}SMe_2$, which was utilized in *Piguel*'s work, proved to be inefficient for the alkynylation reaction with the challenging *gem*-dichloroalkene **94a**.

With these optimized conditions in hand, we set out to explore the alkynylation of 5-heteroaryloxazoles **8b**–**d**.

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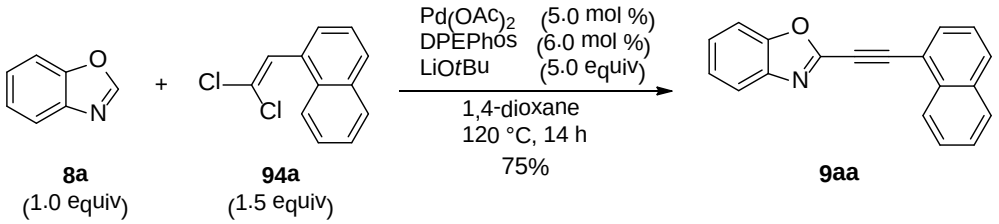
[109] (a) I.-T. Trotuş, T. Zimmermann, F. Schüth, *Chem. Rev.* **2014**, *114*, 1761–1782; (b) Y. Yamamoto, *Chem. Soc. Rev.* **2014**, *43*, 1575–1600; (c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, *114*, 1783–1826.

[110] (a) E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2017; (e) A. Orita, J. Otera, *Chem. Rev.* **2006**, *106*, 5387–5412.

[111] A. J. Zapata, J. Ruíz, *J. Organomet. Chem.* **1994**, *479*, C6–C8.

[112] (a) F. Ramirez, N. B. Desai, N. McKelvie, *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747; (b) E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

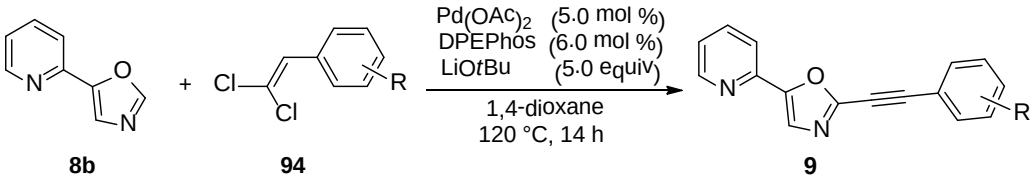


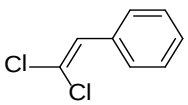
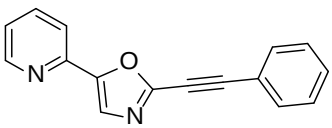
Scheme 46: Optimized reaction conditions for direct alkynylations of benzoxazole **8a** with *gem*-dichloroalkene **94a**.

3.1.1 Scope of Alkynylations of Oxazoles

As shown in Table 1, reactions of 5-(pyridin-2-yl)oxazole (**8b**) with *gem*-dichloroalkenes **94** bearing phenyl **94b**, naphthalene-1-yl **94a** or even tricyclic anthracen-9-yl **94c** substituents smoothly proceeded affording **9ba**–**bc** in moderate to good yields (entries 1–3). Sterically congested *ortho*-substituted arene moieties in *gem*-dichloroalkenes turned out to be well tolerated in these transformations. *ortho*-Tolyl-**9d** and mesityl-substituted **9be** alkynes were obtained in 70% and 67% yield, respectively. However, electron-donating substituents at the *para*-position, such as methyl **94f** and methoxy **94g**, led to relatively low yields. As to electron-withdrawing substituents, halides afforded satisfactory results (entries 8–10), but substrates **94k** or **94l** with a trifluoromethyl and a nitro group, respectively, were not able to undergo the alkynylation reactions (entries 11 and 12).

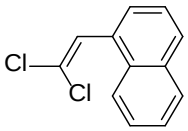
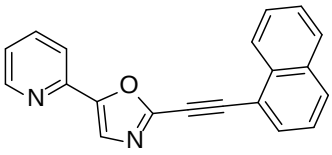
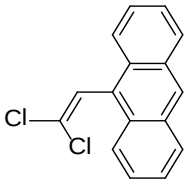
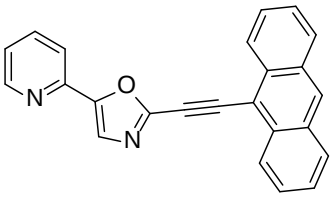
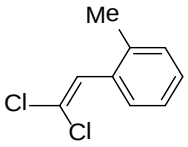
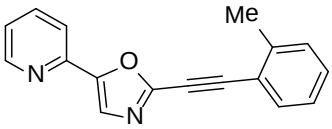
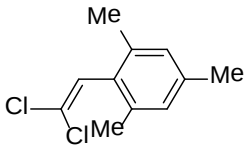
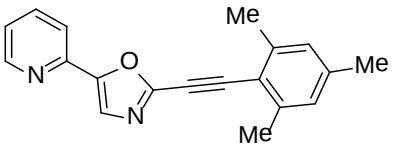
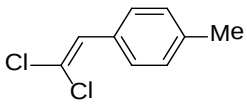
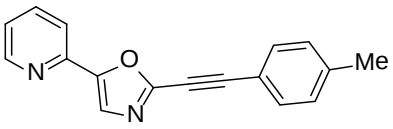
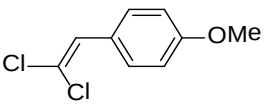
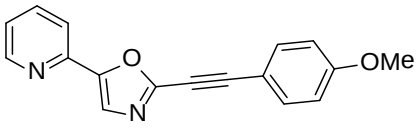
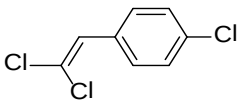
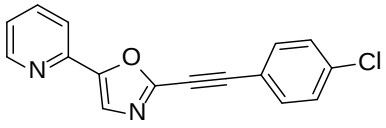
Table 1: Palladium-catalyzed C–H alkynylations of 5-(pyridin-2-yl)oxazole (**8b**).[a]



Entry	*gem*-Dichloroalkene	Product	Yield [%]
1	 **94b**	 **9bb**	64

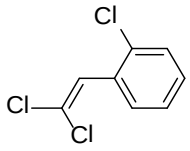
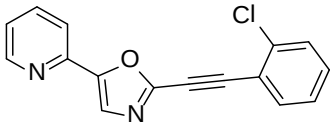
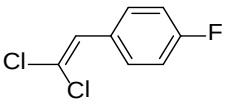
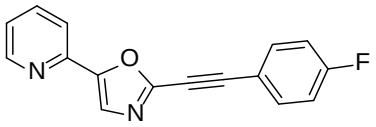
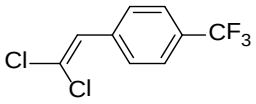
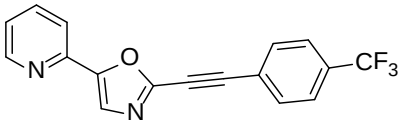
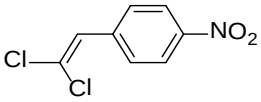
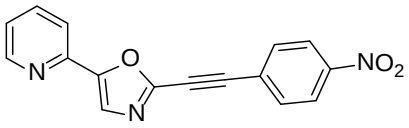
(continued)

(continued)

Entry	*gem*-Dichloroalkene	Product	Yield [%]
2	 **94a**	 **9ba**	88
3	 **94c**	 **9bc**	61
4	 **94d**	 **9bd**	70
5	 **94e**	 **9be**	67
6	 **94f**	 **9bf**	42
7	 **94g**	 **9bg**	38
8	 **94h**	 **9bh**	50

(continued)

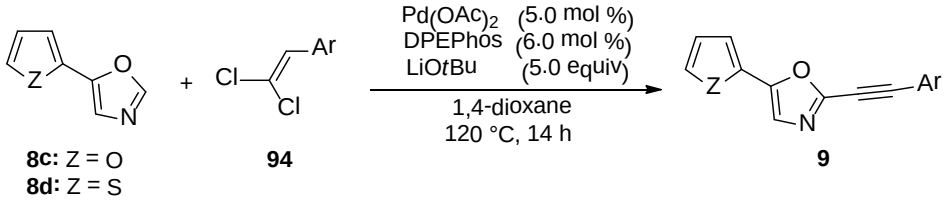
(continued)

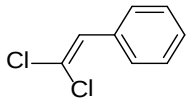
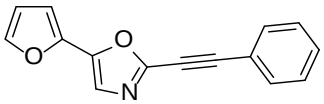
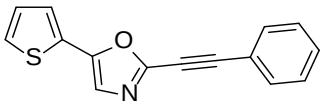
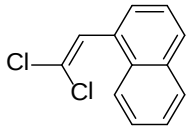
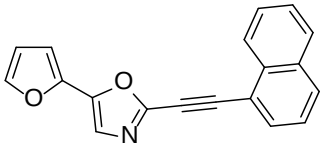
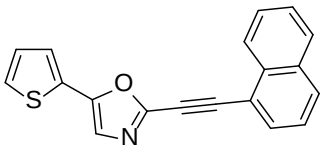
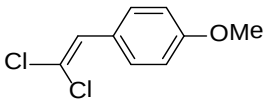
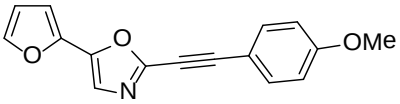
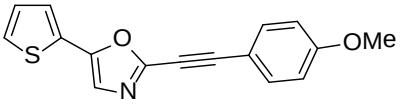
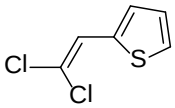
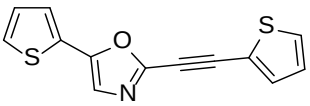
Entry	*gem*-Dichloroalkene	Product	Yield [%]
9	 **94i**	 **9bi**	57
10	 **94j**	 **9bj**	46
11	 **94k**	 **9bk**	0
12	 **94l**	 **9bl**	0

[a] Reaction conditions: **8b** (0.50 mmol), **94** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol %), DPEPhos (6.0 mol %), Li*O*t*Bu (2.50 mmol), 1,4-dioxane (2.0 mL), 120 °C, 14 h; yield of the isolated product.

Oxazoles **8** without a pyridyl substituent, but with other heteroaryl groups (Table 19), such as furyl (entries 1, 3, 5) or thienyl groups (entries 2, 4, 6, 7) appeared to be good candidates for the direct alkynylations. Notably, among aryl groups in *gem*-dichloroalkenes **94**, compound **94a** with a naphthyl group always showed a comparably high reactivity (entries 3 and 4). Interestingly, this approach was also compatible with 2-(2,2-dichlorovinyl)thiophene (**94m**), giving rise to a synthetically useful dithiophene **9cm** in 35% yield (entry 7).

Table 2: Palladium-catalyzed C–H alkynylations of oxazole **8c** or **8d**.[a]

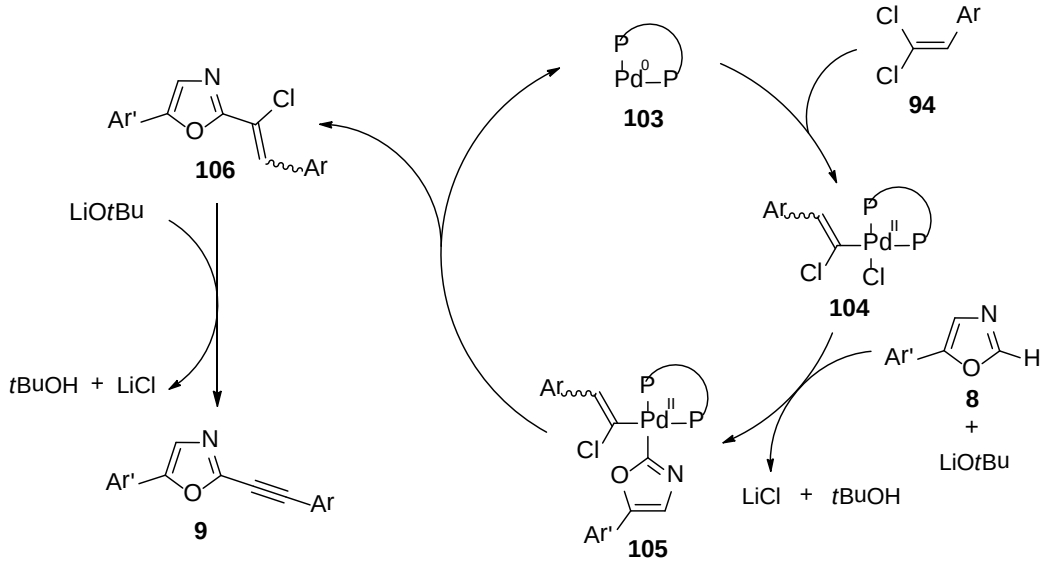


Entry	*gem*-Dichloroalkene	Product	Yield [%]
1	 **94b**	 **9cb**	46
2	**94b**	 **9db**	52
3	 **94a**	 **9ca**	77
4	**94a**	 **9da**	66
5	 **94g**	 **9cg**	57
6	**94g**	 **9dg**	57
7	 **94m**	 **9dm**	35

[a] Reaction conditions: **8** (0.50 mmol), **94** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol %), DPEPhos (6.0 mol %), LiO*t*Bu (2.50 mmol), 1,4-dioxane (2.0 mL), 120 °C, 14 h; yield of the isolated product.

3.1.2 Proposed Catalytic Cycle

Analogously to the mechanism proposed by *Piguel*, two possible reaction pathways could be envisioned (Scheme 6). Since Piguel did not observe the potential intermediate alkenyloxazole **14**, she considered the one by initial formation of alkynyl bromides **6** by dehydrobromination to be most reasonable (Scheme 6, path B). However, under our reaction conditions, the intermediate alkenyloxazole **106** was clearly detected in GC/MS, and this indicated that another pathway seemed to be more likely involved. Thereby, the alternative catalytic cycle for the palladium-catalyzed C–H alkynylation with the *gem*-dichloroalkene **94** is proposed (Scheme 47). The presence of two geminal chlorine atoms in the *gem*-dichloroalkene **94** renders the alkene reactive towards oxidative addition to palladium(0) complex **103**. After the C–H metalation,[113] oxazole replaces the chloride *via* ligand-exchange to give the palladium(II) species **105**. A subsequent reductive elimination leads to the intermediate **106** and regenerates the catalytically active palladium(0) complex **103**. The final dehydrochlorination affords the desired alkynylated product **9**.



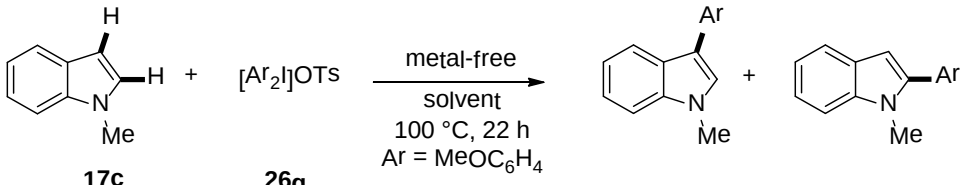
Scheme 47: Mechanistic proposal for palladium-catalyzed C–H alkynylations of oxazoles **8**.

[113] (a) B. Liégault, I. Petrov, S. I. Gorelsky, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 1047–1060; (b) L. Théveau, C. Verrier, P. Lassalas, T. Martin, G. Dupas, O. Querolle, L. V. Hijfte, F. Marsais, C. Hoarau, *Chem. Eur. J.* **2011**, *17*, 14450–14463.

3.2 Metal-Free Direct Arylations of Indoles with Diaryliodonium Salts

Significant progress was accomplished in transition metal-catalyzed direct arylations of indoles utilizing diaryliodonium salts **26** as arylating reagents. Moreover, some efforts were recently made to elaborate efficient direct arylations of electron-rich nitrogen heterocycles in the absence of transition metal catalysts.[63–66]

Over the past decade, *Ackermann*'s group devoted much effort to develop the novel indole syntheses *via* intermolecular annulation or palladium-catalyzed direct arylation. More recently, a convenient metal-free C3-arylation of indoles **17** with diaryliodonium tosylates **26** was established. In this work, the authors observed that in several cases a small amount of starting material **17c** was converted to the C2-arylated indole **20cg** (Table 3).



Solvent	**24cg** (Yield [%])	**20cg** (Yield [%])
DMF:	56	11
toluene:	55	12
1,4-dioxane:	43	9

Table 3: Regioselectivity of metal-free direct arylations.

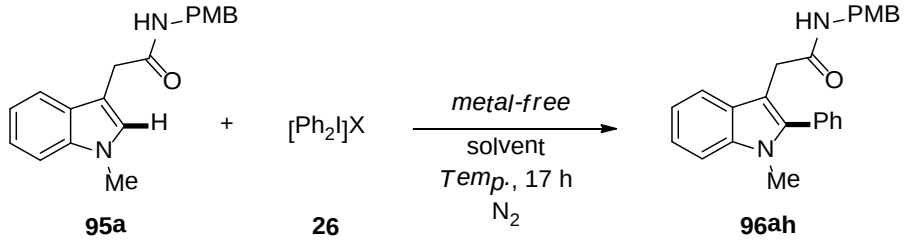
Hence, it was considered whether the C2-arylation of indoles can be promoted with the assistance of a directing group at the C3 position of the substrates. With this in mind, we set out to develop a metal-free carboxamide-directed C2-arylation of indoles **95** with diaryliodonium salts **26**.

3.2.1 Optimization Studies

At the outset of our studies, we chose carboxamide as the directing group and treated 2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) with [Ph_2I]OTs (**26h**) (Table 4). The reaction was highly dependent on the reaction temperature (entries 1–6). We were pleased to discover that the C2-arylated indole **96ah** was provided in 90% yield at a reaction temperature of 100 °C (entry 4). Subsequently, a range of counteranions in diphenyliodonium salts was explored. While the counteranions triflate and tetrafluoroborate afforded 2-phenylindole **96ah** in moderate yields (entries 7 and 8), the relatively more basic trifluoroacetate as the

counteranion provided only traces of the product **96ah** (entry 9). After probing several solvents, DMF was found to be optimal for arylations (entries 10 and 11). Further increasing of the amount of diphenyliodonium tosylates (**26h**) raised the reaction yield to 96% (entry 13).

Table 4: Optimization of metal-free direct arylations of the indole **95a**.[a]



95a **26** **96ah**

Entry	X	Solvent	*Temp.* [°C]	Yield [%]
1	OTs	DMF	23	0
2	OTs	DMF	40	18[b]
3	OTs	DMF	60	25[b]
4	OTs	DMF	80	70
5	OTs	DMF	100	90
6	OTs	DMF	120	75
7	OTf	DMF	100	70
8	BF_4	DMF	100	71
9	TFA	DMF	100	11[b]
10	OTs	DCE	100	78
11	OTs	toluene	100	71
12[c]	OTs	DMF	100	95
13[d]	**OTs**	**DMF**	**100**	**96**

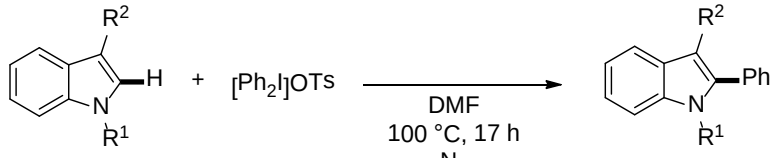
[a] Reaction conditions: **95a** (0.50 mmol), **26** (0.55 mmol), solvent (2.0 mL), 17 h, yield of isolated product. [b] GC conversion. [c] **26** (0.65 mmol). [d] **26** (0.75 mmol).

3.2.2 Effect of C3-Substitutents on C2-Arylations of Indoles

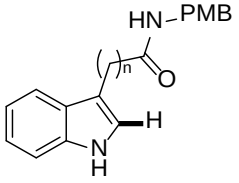
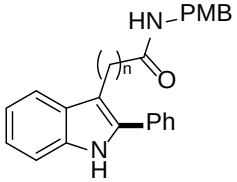
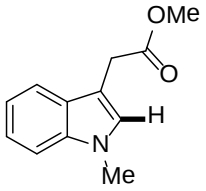
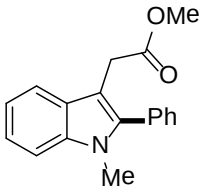
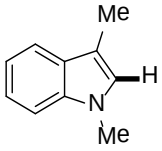
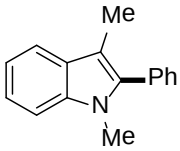
Furthermore, the effect of the substituents at the C3 position on the C2-arylations of indoles **95** was examined (Table 5). While the indolylacetamide **95c** was efficiently converted to the desired C2-arylated product **96ch**, the homologues **95b** or **95d** displayed a significantly

reduced reactivity. A comparable observation was made with the corresponding ester **95e** or simple the 3-methyl derivative **95f**, thereby highlighting a considerable assistance exerted by the amide functionality.

Table 5: Variation of substitution pattern at C3 position of indoles **95**.[a]



95b-f **26h** **96bh-fh**

Entry	Indole	Product		Yield [%]
1			n = 2: **96bh**	22
2			n = 1: **96ch**	90
3			n = 0: **96dh**	0
	95b-d			
4				0
	95e	**96eh**		
5				0
	95f	**96fh**		

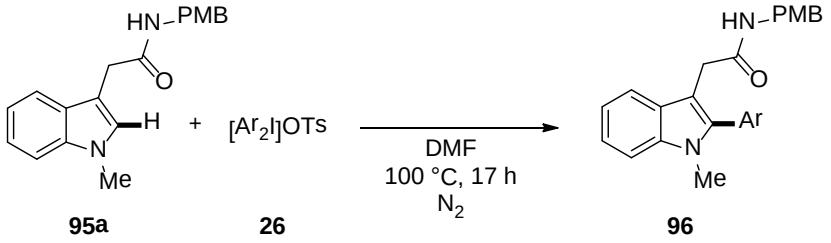
[a] Reaction conditions: **95** (0.50 mmol), **26h** (0.75 mmol), DMF (2.0 mL), 100 °C, 17 h; yield of isolated product.

3.2.3 Scope of Metal-Free C–H Arylations of Indolylacetamides

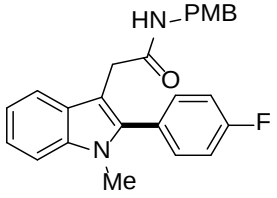
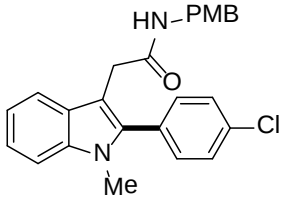
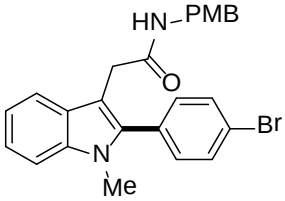
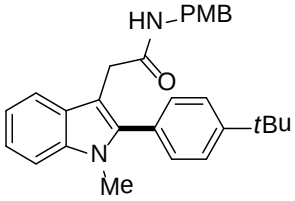
With the optimized reaction conditions in hand, we examined the scope of the diaryliodonium tosylates **26** (Table 6). Both electron-rich and electron-deficient arenes were found to be suitable coupling partners for this reaction (entries 1–5). In particular, halogen-containing motifs were well tolerated, which provided the potential for further cross-coupling transformations. The steric hindrances caused by an *ortho*-methyl group in tosylate **26m**

reduced the yield of **96am** to 63% (entry 6), and the additional steric obstacles in more bulky arylating reagent **26n** suppressed the reaction completely (entry 7). Notably, this arylation protocol was also compatible with the heteroaromatic dithienyliodonium tosylate (**26o**) (entry 8).

Table 6: Scope of diaryliodonium tosylates **26**.[a]

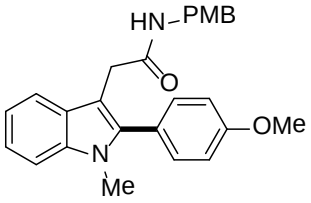
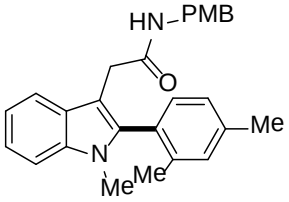
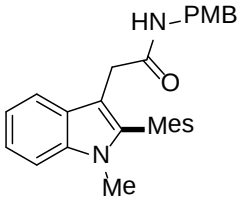
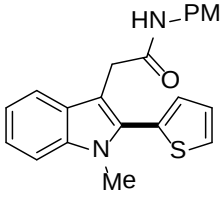


95a **26** **96**

Entry	Ar	Product	Yield [%]
1	4-FC_6H_4 **26i**	 **96ai**	95
2	4-ClC_6H_4 **26j**	 **96aj**	89
3	4-BrC_6H_4 **26k**	 **96ak**	93
4	4-*t*BuC_6H_4 **26el**	 **96al**	83

(continued)

(continued)

Entry	Ar	Product	Yield [%]
5	4-$MeOC_6H_4$ **26g**	 **96ag**	84
6	2,4-$Me_2C_6H_3$ **26m**	 **96am**	63
7	2,4,6-$Me_3C_6H_2$ **26n**	 **96an**	0
8	2-thienyl **26o**	 **96ao**	65

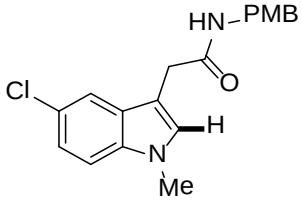
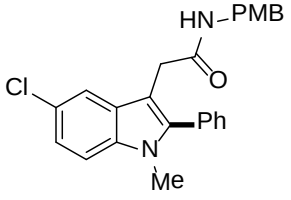
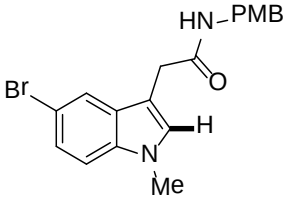
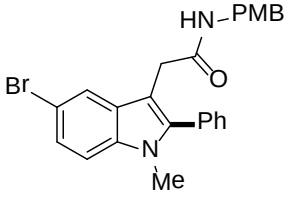
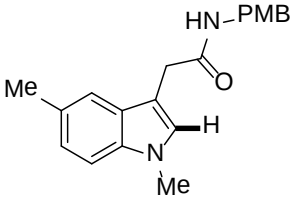
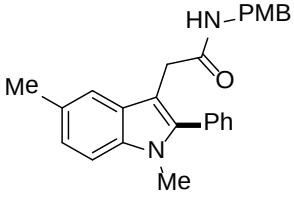
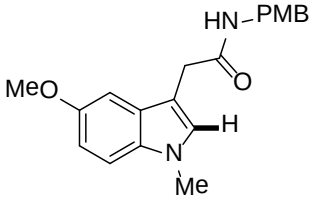
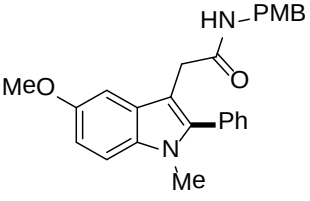
[a] Reaction conditions: **95a** (0.50 mmol), **26** (0.75 mmol), DMF (2.0 mL), 100 °C, 17 h; yield of the isolated product.

We next turned our attention to the introduction of diverse substituents onto the indole core (Table 7). Initial examinations of substitutions on the benzene ring of the indole motif demonstrated that the electron-donating groups were beneficial for the C2-arylation. Electron-withdrawing substituents decreased the yield of **96gh** and **96hh** (entries 1 and 2). In contrast, methyl and methoxyl groups facilitated the C–H functionalization (entries 3 and 4). With respect to the alkyl groups on the indole nitrogen, the *N*-benzyl-, *N*-butyl- and *N*-octylindole-3-acetamides **95k**–**m** delivered the 2-arylindole **96kh**–**mh** in good to excellent yields (entries 5–7). The 1-tosylindole **95n** was completely inert under the reaction condition (entry 8), thus indicating the importance of the high electron density in the indole ring. Furthermore, the examination of substituents in the directing group revealed that the primary,

secondary and tertiary acetamides **95o**–**q** enabled the C2-arylation in moderate to excellent yields (entries 9–11). Notably, when a pyridinyl group was embedded into a potential bidentate directing group, no desired product was observed (entry 12).

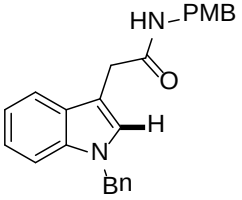
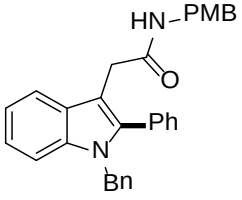
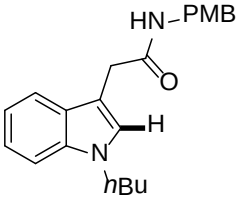
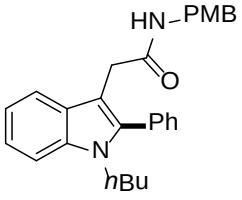
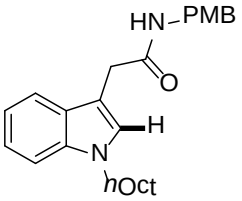
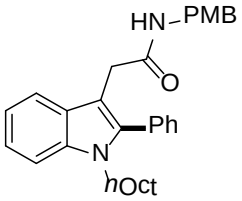
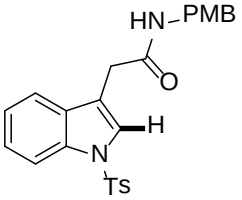
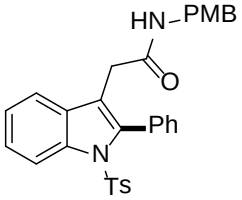
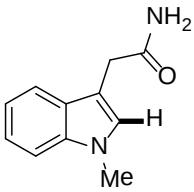
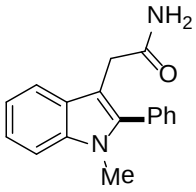
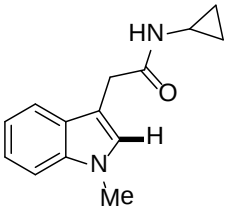
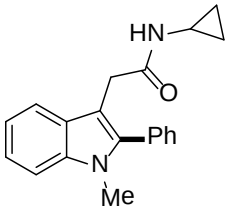
Table 7: Scope of indole substrates **95**.[a]

95 **26h** **96**

Entry	Indole	Product	Yield [%]
1	 **95g**	 **96gh**	48
2	 **95h**	 **96hh**	56
3	 **95i**	 **96ih**	91
4	 **95j**	 **96jh**	87

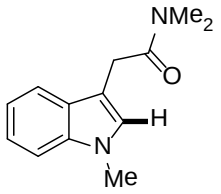
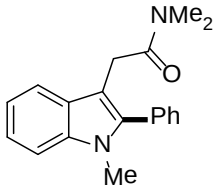
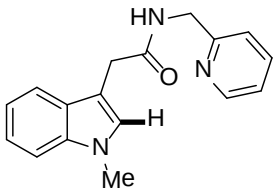
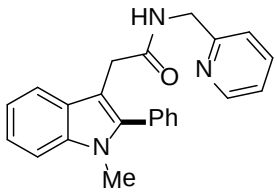
(continued)

(continued)

Entry	Indole	Product	Yield [%]
5	 **95k**	 **96kh**	86
6	 **95l**	 **96lh**	93
7	 **95m**	 **96mh**	73
8	 **95n**	 **96nh**	0
9	 **95o**	 **96oh**	76
10	 **95p**	 **96ph**	98

(continued)

(continued)

Entry	Indole	Product	Yield [%]
11	 **95q**	 **96qh**	96
12	 **95r**	 **96rh**	0

[a] Reaction conditions: **95** (0.50 mmol), **26h** (0.75 mmol), DMF (2.0 mL), 100 °C, 17 h; yield of the isolated product.

According to these results, it can be estimated that the high reactivity towards arylation was crucially dependent on four factors, namely the reaction temperature, the assistance of an acetamide functionality, the electronic nature of the indole and the steric hindrance of the arylating reagent.

3.2.4 Mechanistic Studies

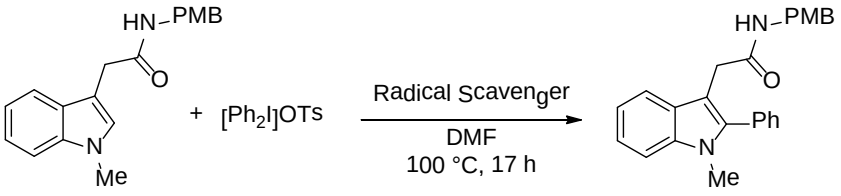
3.2.4.1 Reactions with Radical Inhibitors and Radical Clock

In consideration of the unique selectivity and the outstanding efficacy of our metal-free arylation, we became interested in delineating its mode of action. In order to examine the possibility of a radical mechanism, radical inhibition tests were carried out utilizing the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) [114] and 2,6-di-*tert*-butyl-4-methylphenol (BHT),[115] both of which are well known to be effective radical scavengers. A reaction in the presence of the former smoothly afforded the C2-arylated product **96ah** in 56% yield, along with 34% of the reisolated starting material **95a** (Scheme 48). Furthermore, BHT actually

[114] (a) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 10795–10798; (b) X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330–10333.

[115] S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996–6005.

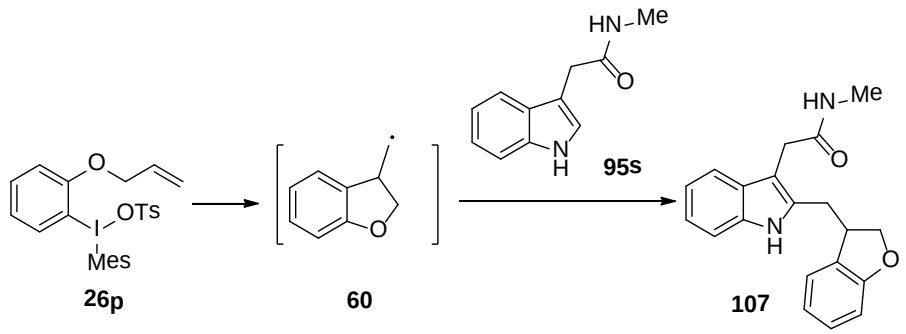
displayed no negative effect on the reaction course. These findings indicated that a SET-type radical reaction[70c,71] was less likely to be operative in this arylation protocol.



Radical scavenger	Yield of **96ah**	**95a** [%]
1.5 equiv TEMPO:	53	34
1.5 equiv BHT:	96	0

Scheme 48: Effects of radical inhibitors on the reaction efficiency.

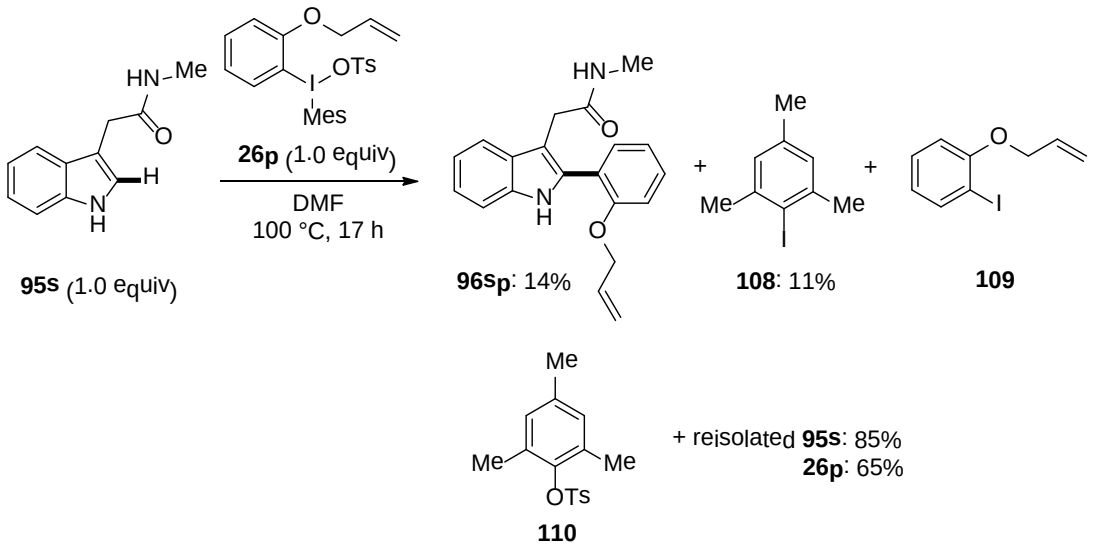
Moreover, additional data obtained by utilizing a "radical clock" test were also indicative of the absence of a radical mechanism. An unsymmetrical diaryliodonium tosylate **26p** containing an *O*-allyl moiety as a potential radical clock precursor[74,116] was employed for arylation of indolylacetamide **95s**. If the reaction proceeded *via* a radical pathway, the intermediate (2,3-dihydrobenzofuran-3-yl)-methyl radical (**60**) may react with the indolylacetamide **95s** affording alkylated indoles of type **107** (Scheme 49).



Scheme 49: Possible byproduct of arylation with λ^3-iodane **26p** *via* radical reaction pathway.

Indeed, no corresponding byproduct **107** was formed, as determined by ^{1}H NMR of the crude reaction mixture after completion of the reaction. On the contrary, the usual C2-arylated indole **96sp** was obtained in 14% yield (Scheme 50). Another part of **26p** decomposed, thereby furnishing *o*-(allyloxy)iodobenzene (**109**) and tosyloxymesitylene (**110**).[117]

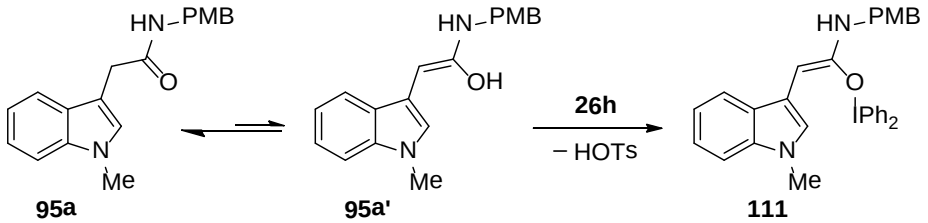
[116] I. Sokolovs, D. Lubriks, E. Suna, *J. Am. Chem. Soc.* **2014**, *136*, 6920–6928.
[117] A mixture of **109** and **110** was isolated in 30% yield after flash chromatography; the ratio of the products was estimated by GC to be 1:1.



Scheme 50: Arylation with the potential radical clock precursor **26p**.

3.2.4.2 Probing *α*-Substituted Indolylacetamides

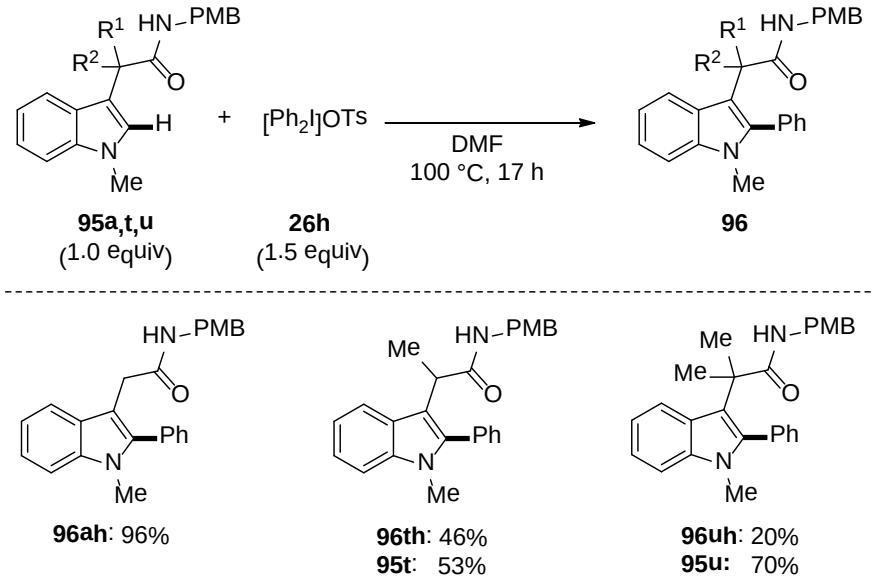
Koser's[118] or *Quideau*'s[119] studies demonstrated that a ligand exchange step, namely replacing the counteranion with the enolate fragment, took place in a phenylation reaction of a *α*-carbonyl compound with a hypervalent iodine (III) salt. Hence, α-substituted indolylacetamides were synthesized to get insight into the feasibility of a S_N2-type replacement of a tosylate anion in the diphenyliodonium tosylate (**26h**) by the enol moiety of **95a'**, which could be formed from **95a** *via* keto-enol-tautomerism (Scheme 51).



Scheme 51: Possible coordination of enol **95a'** to the diaryliodonium salt **26h**.

As shown in Scheme 52, the yields of arylated indoles **96** decreased dramatically along with the consecutive incorporation of methyl groups at the α-position of the acetamide. However, the arylated product from *α*,*α*-dimethyl-indolylacetamide **95u** was still provided in 20% yield, which renders a substitution by an enol less likely to be operative.

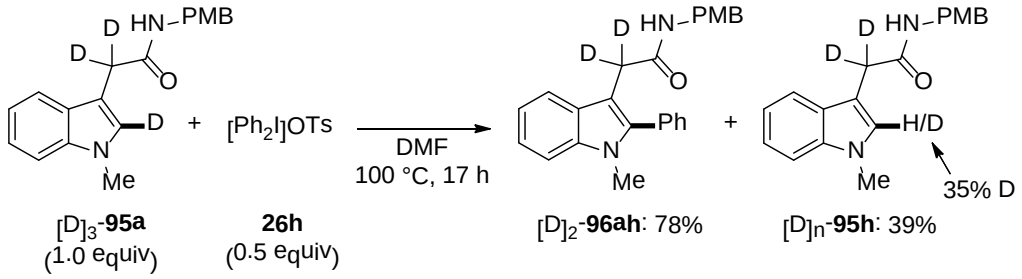
[118] K. Chen, G. F. Koser, *J. Org. Chem.* **1991**, *56*, 5764–5767.
[119] A. Ozanne-Beaudenon, S. Quideau, *Angew. Chem. Int. Ed.* **2005**, *44*, 7065–7069.



Scheme 52: Arylation of α-substituted indolylacetamides **95a**,**t**,**u**.

3.2.4.3 H/D Exchange Study

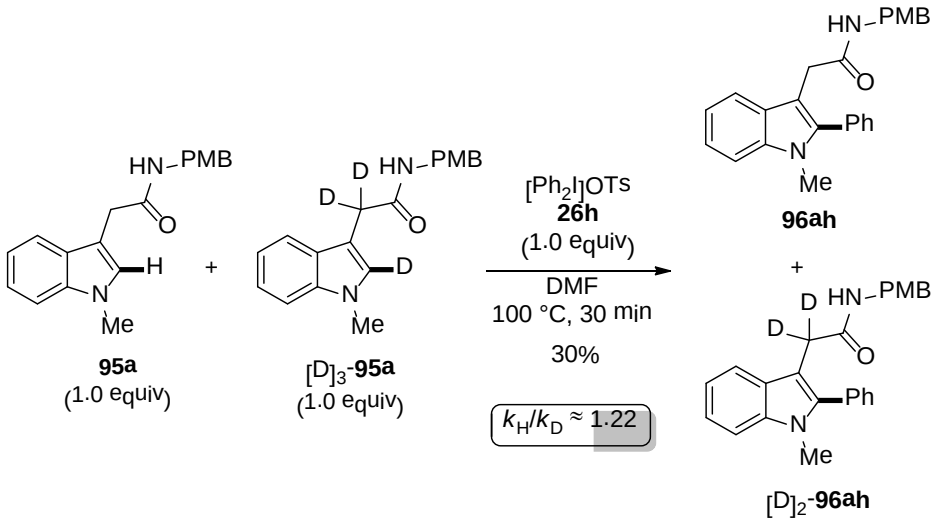
The arylation reaction of deuterated indolylacetamide $[D]_3$-**95a** in twofold excess with $[Ph_2I]OTs$ (**26h**) in DMF afforded starting material $[D]_n$-**95a** as well as the product $[D]_2$-**96aa** (Scheme 53). Isolation of the former compound revealed a reversible H/D-exchange reaction at the C2 position of the indole moiety. Meanwhile, the retention of deuterium at the α-position in both $[D]_n$-**95a** and $[D]_2$-**96ah** indicated that a keto-enol-tautomerism did not occur during the course of the reaction, and thus disproved a mechanism with initial coordination of the enol **95a'** to the diphenyliodonium tosylate (**26h**) (Scheme 51).



Scheme 53: H/D exchange study.

3.2.4.4 Kinetic Isotope Effect

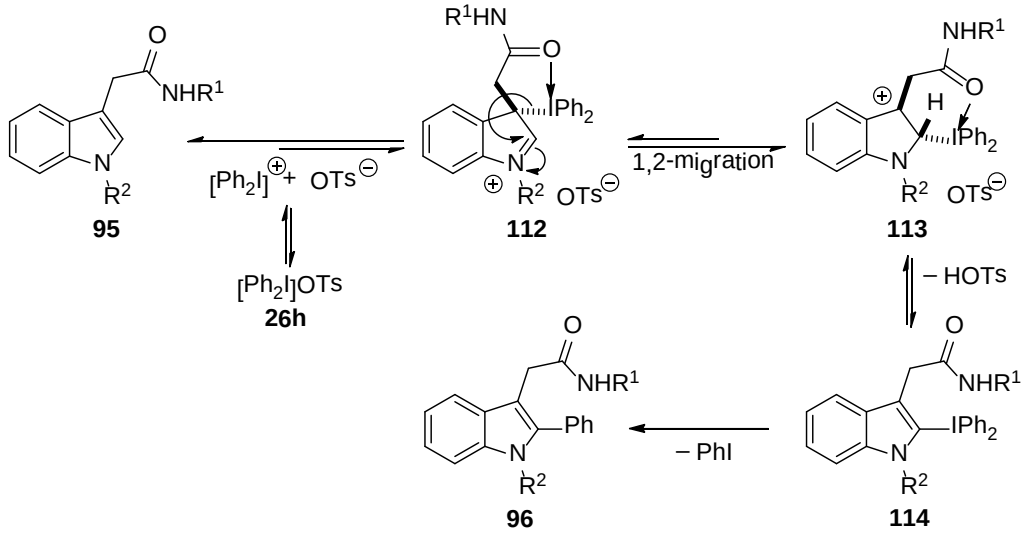
The intermolecular competition experiment between substrates **95a** and $[D]_3$-**95a** indicated a rather low kinetic isotope effect (KIE) of $k_H/k_D \approx 1.22$ (Scheme 54). This finding highlighted that the cleavage of the C–H bond was not involved in the rate-limiting step.



Scheme 54: KIE study of arylation reaction with substrates **95a** and $[D]_3$-**95a**.

3.2.4.5 Proposed Mechanism

Based on the mechanistic studies, a directing group-assisted S_EAr-type mechanism was proposed to account for the site-selective metal-free direct arylation of indolylacetamide with diaryliodonium salt (Scheme 55).



Scheme 55: Proposed mechanism.

Initially, a thermally induced dissociation of the hypervalent iodine(III) salt **26** likely takes place, providing an electrophilic diaryliodonium cation and a counteranion. Thereafter, the diaryliodonium cation is attacked by the C3 position of indole **95** to form iminium tosylate **112**. Because of the steric hindrance stemming from the C3-substituent as well as of the temporary loss of aromaticity, the intermediate **112** would reversibly be converted back to the starting materials. Meanwhile, this steric effect forces the intermediate **112** to undergo an

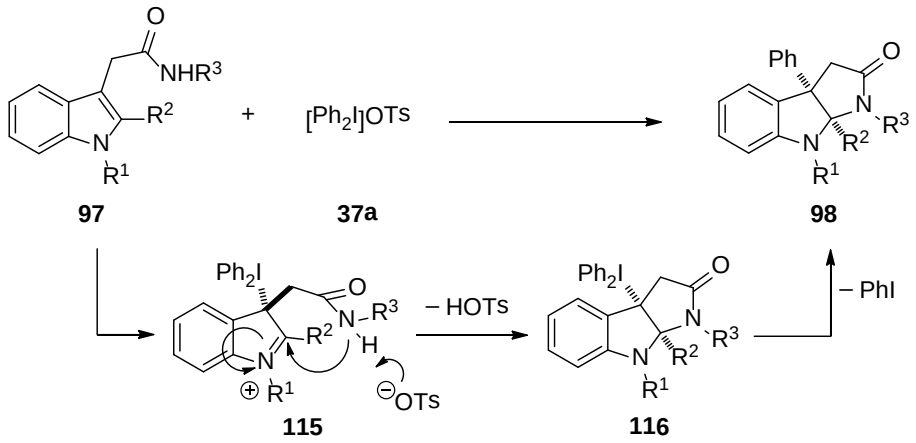
acetamide moiety-assisted C3→C2 migration of the diphenyliodinyl substituent, affording the intermediate **113**. After the abstraction of a proton by the tosylate, an instable tris(hetero)aryliodane species **114** is formed, which decomposes to the final product **96** *via* a reductive elimination.

The 1,2-migration step of the λ^3-iodane is supported by the experimental data published from other groups. Based on kinetic studies for the C2-azo-coupling reaction of 3-methylindole with *p*-nitrobenzenediazonium tetrafluoroborate, which is also an excellent electrophile. *Jackson* postulated an initial addition of the electrophile at the C3-position of 3-methylindole with subsequent migration to the C2 atom.[120] More recently, *Lera*'s computational studies demonstrated the migratory pathway in the construction of hexahydropyrrolo[2,3-*b*]indoles *via* the phenylselenation-cyclization cascade reaction of tryptophans.[121]

[120] A. H. Jackson, P. P. Lynch, *J. Chem. Soc. Perkin Trans. 2* **1987**, *12*, 1483–1487.
[121] C. S. López, C. Pérez-Balado, P. Rodríguez-Graña, Á. R. de Lera, *Org. Lett.* **2008**, *10*, 77–80.

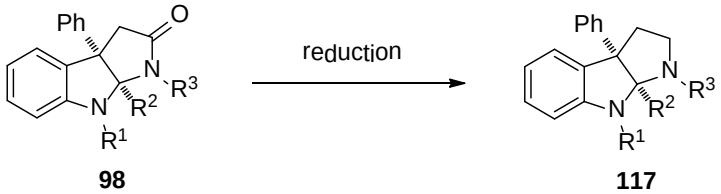
3.3 Metal-Free Synthesis of Aryl Pyrroloindolines

Our previous studies (Chapter 3.2.4) indicated that the diphenyliodonium salt **26** as the reactive electrophile should undergo the functionalization at the C3 position of indolylacetamide **95** affording the iminium salt **112**, the diphenyliodinyl(III) substituent of which could migrate from C3 to C2 (Scheme 55). According to this mechanism, it can be assumed that a substitution at the C2 position of indole could prevent such a C3→C2 migration in the iminium intermediate **115**, as outlined in Scheme 56. After the formation of the trivalent iodine intermediate **115**, the amide functionality should attack the iminium ion within an intramolecular cyclization. The final reductive elimination should afford the cyclization product pyrroloindolone **98**. Given the architectural constraint of the intermediate **116**, it can be expected that the functional group R^2 in the final product **98** should be *cis*-located with respect to the new phenyl group.



Scheme 56: Proposed reaction pathway of the arylation-cyclization cascade.

Finally, the pyrroloindolone **98** can easily be converted to the pyrroloindoline **117** through a simple reduction (Scheme 57).

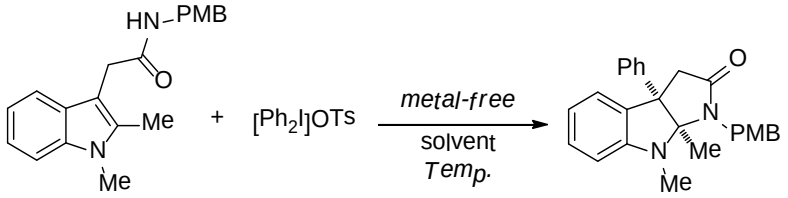


Scheme 57: Reduction of pyrroloindolone **98** to pyrroloindoline **117**.

3.3.1 Optimization Studies

The feasibility of the proposed arylation-cyclization cascade was examined by testing reactions of indolylacetamide **97a** with diphenyliodonium tosylate **26h** at different reaction temperatures and in various solvents. As shown in Table 8, the temperature of 100 °C was revealed to be optimal for this metal-free arylation-cyclization cascade reaction (entries 1–4). Further experiments (entries 3, 5–8) indicated DMF as the optimal reaction solvent, in which the desired product **98ah** was obtained in 89% yield (entry 3).

Table 8: Evaluation of reaction conditions



97a **26h** **98ah**

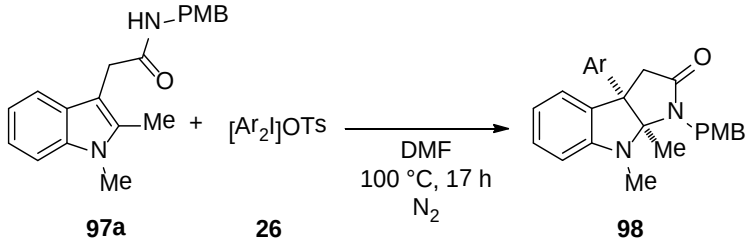
Entry	Solvent	*Temp.* (°C)	Yield [%]
1	DMF	23	0
2	DMF	80	55
3	**DMF**	**100**	**89**
4	DMF	120	79
5	DCE	100	32
6	1,4-dioxane	100	42
7	toluene	100	55
8	NMP	100	73

[a] Reaction conditions: **97a** (0.50 mmol), **26h** (0.75 mmol), solvent (2.0 mL), 17 h; yield of the isolated product.

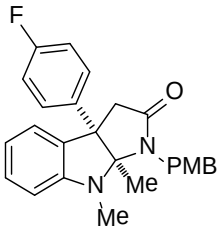
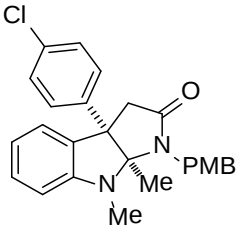
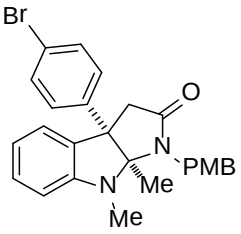
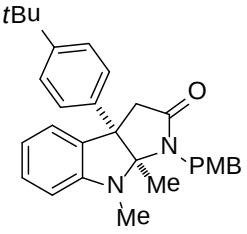
3.3.2 Scope and Limitations

Under the optimized reaction conditions, a broad range of diaryliodonium salts **26** was tested and exhibited satisfactory to very good results (Table 9). Thus, the electrophilicity of the arylating agent **26** appeared to exert only a minimal influence on the cyclization-arylation cascade reaction. Iodonium salts with both electron-rich and electron-deficient aryl groups afforded pyrroloindolones **98** in good yields (entries 1–5).

Table 9: Metal-free arylation-cyclization cascade reactions.[a]

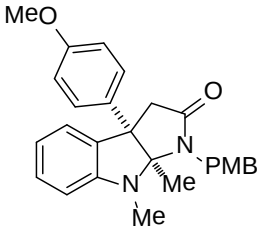


97a **26** **98**

Entry	Ar	Product	Yield [%]
1	4-FC_6H_4 **26i**	 **98ai**	81
2	4-ClC_6H_4 **26j**	 **98aj**	83
3	4-BrC_6H_4 **26k**	 **98k**	79
4	4-*t*BuC_6H_4 **26l**	 **98al**	85

(continued)

(continued)

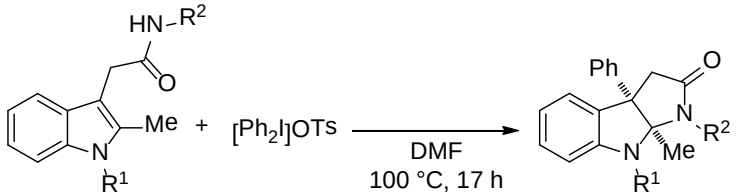
Entry	Ar	Product	Yield [%]
5	4-$MeOC_6H_4$ **26g**	 **98ag**	83

[a] Reaction conditions: **97a** (0.50 mmol), **26** (0.75 mmol), DMF (2.0 mL), 17 h; yield of the isolated product.

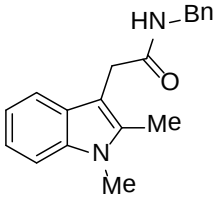
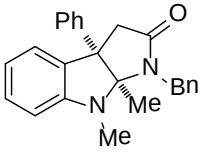
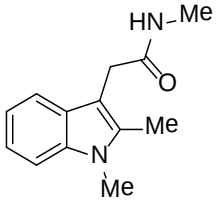
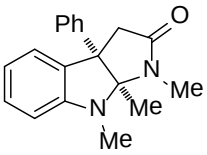
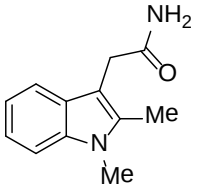
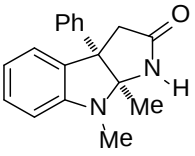
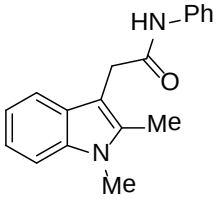
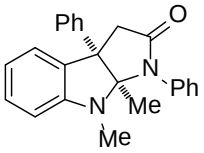
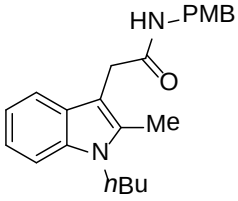
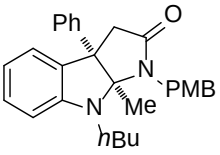
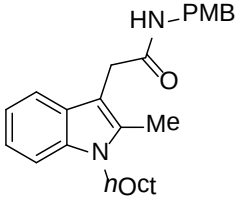
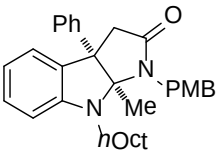
Subsequently, different substituent patterns in the acetamide functionality were examined (Table 10). The arylation-cyclization cascade involving either a monoalkylated or a primary acetamide proceeded with good yields of the desired products (entries 1–3). On the contrary, *N*-phenylacetamide **97e** afforded product **98eh** in only 53% yield, presumably due to the lower nucleophilicity of the acetamide nitrogen atom (entry 4).

Generally, alkyl substituents on the nitrogen atom of the indole core exerted no influence on the synthesis of pyrroloindolones **98** (entries 5 and 6). The benzyl group, however, appeared to be less suitable for the reaction, what could presumably be attributed to its de steric effect (entry 7). Meanwhile, it was also found that the metal-free arylation-cyclization cascade was not restricted to the *N*-protected substrate, but also could be applied to the free (NH)-indolylacetamide **97i** (entry 8).

Table 10: Scope of metal-free pyrroloindolone synthesis with indoles **97**.[a]

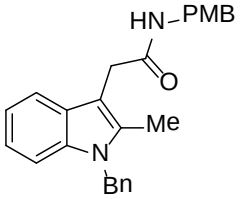
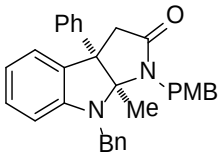
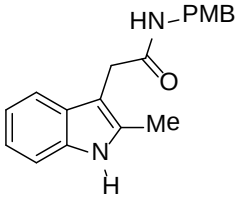
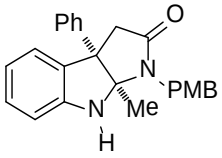


97 **26h** **98**

Entry	Indolylacetamide	Product	Yield [%]
1	 **97b**	 **98bh**	90
2	 **97c**	 **98ch**	86
3	 **97d**	 **98dh**	82
4	 **97e**	 **98eh**	53
5	 **97f**	 **98fh**	82
6	 **97g**	 **98gh**	89

(continued)

(continued)

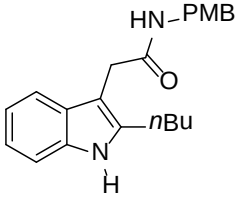
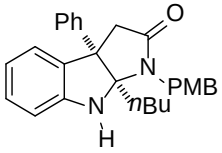
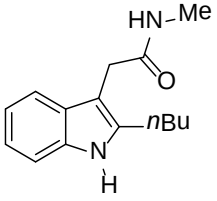
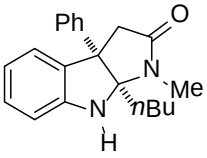
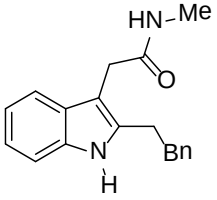
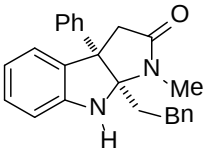
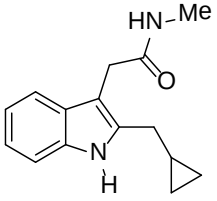
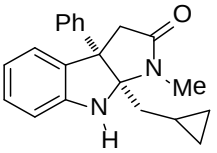
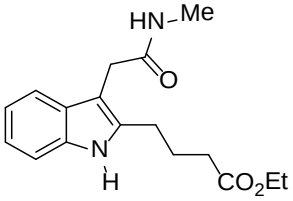
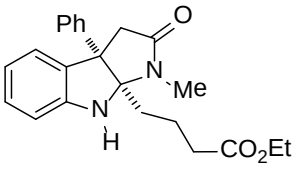
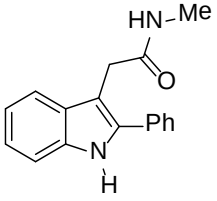
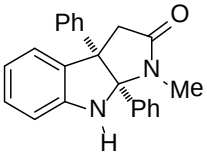
Entry	Indolylacetamide	Product	Yield [%]
7	 **97h**	 **98hh**	53
8	 **97i**	 **98ih**	84

[a] Reaction conditions: **97** (0.50 mmol), **26h** (0.75 mmol), DMF (2.0 mL), 17 h; yield of the isolated product.

As the next important step, the methyl group at the C2 position was replaced by other substituents (Table 11). *n*-Butyl-, phenylethyl-, cyclopropylmethyl- or 4-ethoxy-4-oxobutan-1-yl groups were well tolerated with this reaction protocol (entries 1–5). The reaction of (2-phenyl-1*H*-indol-3-yl)acetamide (**96sh**), which was obtained by metal-free C2-arylation of the corresponding indolylacetamide **95s** (Chapter 3.2), did not provide the desired product **98oh** (entry 6). This result is consistent with those obtained in arylation reactions of indolylacetamides **95** with diaryliodonium salts **26**, in which only the C2-arylated products **96** were obtained (Table 4), whereas the products of their further transformation were not isolated.

Table 11: Scope of metal-free pyrroloindolone synthesis with indoles **97**.[a]

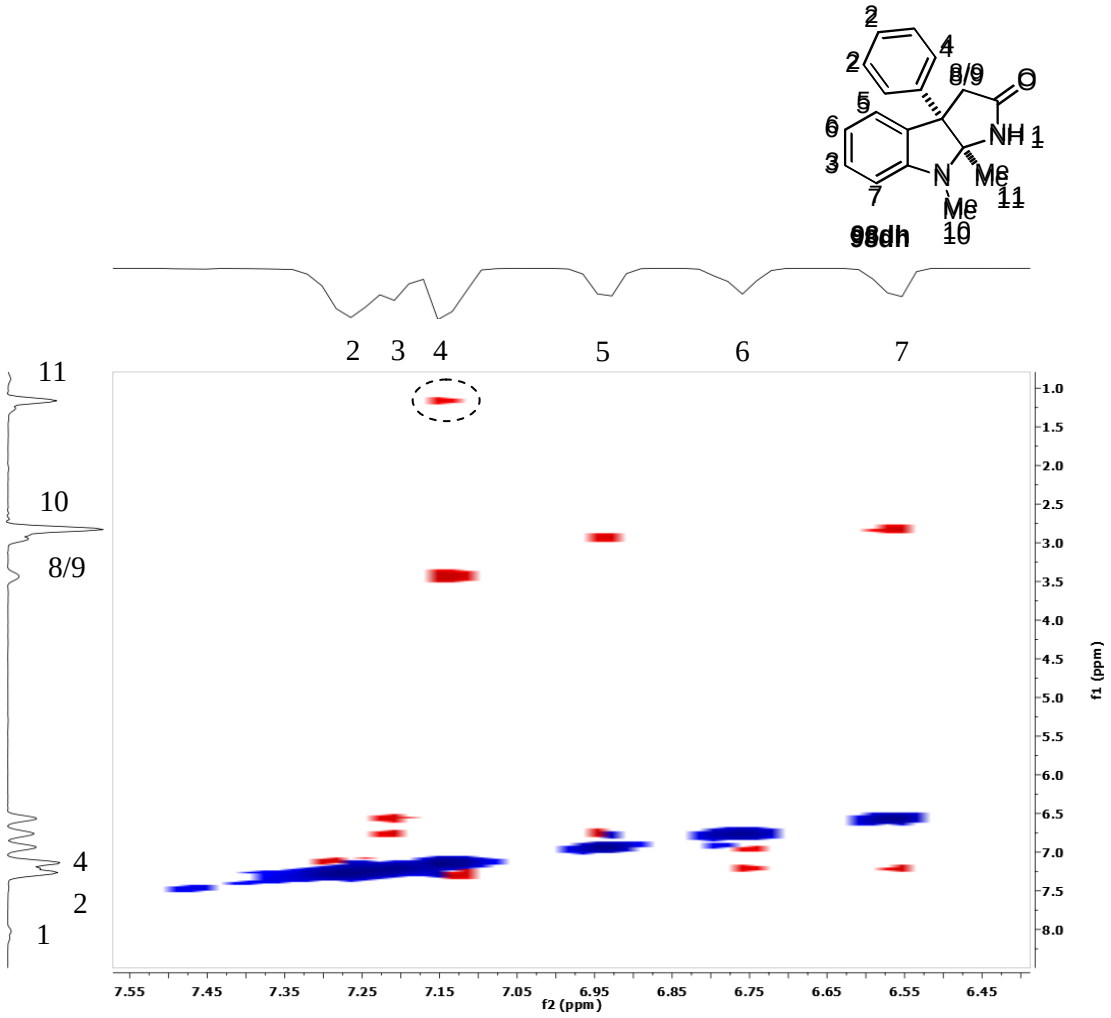
97 **26h** **98**

Entry	Indole	Product	Yield [%]
1	 **97j**	 **98jh**	54
2	 **97k**	 **98kh**	59
3	 **97l**	 **98lh**	66
4	 **97m**	 **98mh**	51
5	 **97n**	 **98nh**	55
6	 **96sa**	 **98oh**	0

[a] Reaction conditions: **97** (0.50 mmol), **26h** (0.75 mmol), DMF (2.0 mL), 17 h; yield of the isolated product.

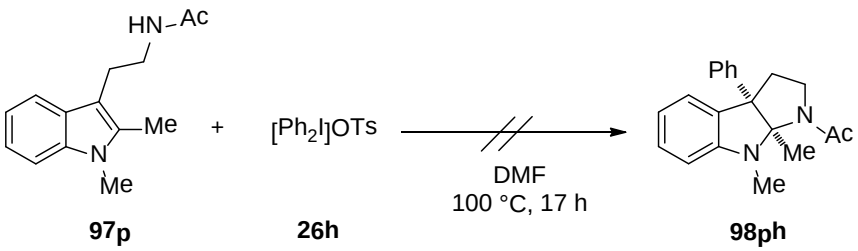
The 2D-NOESY spectrum of the pyrroloindolone **98dh**, as shown in Scheme 58, demonstrated that it existed an interaction between the methyl group (marked with the

number 11) and the phenyl group (marked with the number 4), which confirmed these two groups were *cis* to each other.



Scheme 58: 2D-NOESY spectrum of the pyrroloindolone **98dh**.

The efficacy of the arylation-cyclization cascade is also dependent on the substituent at the C3 position. When in substrate **97p** the acetamide moiety was replaced by the (*N*-acetylamino)ethylene group, no corresponding cyclization product **98ph** was obtained (Scheme 59).

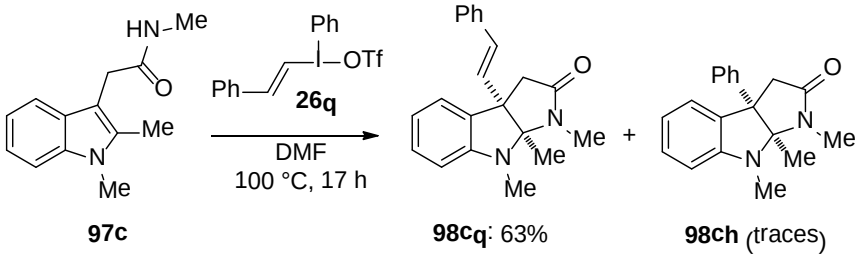


97p **26h** **98ph**

Scheme 59: Failed arylation-cyclization cascade of **97p**.

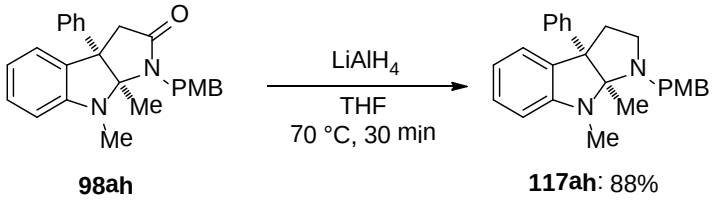
This reaction conditions for the synthesis of C3-arylated pyrroloindolones **98** can also be

applied to alkenylation-cyclization reactions. For instance, reaction with the unsymmetrical (phenyl)(phenylvinyl)iodonium triflate (**26q**) furnished the alkenylated product **98cq** in 63% isolated yield (Scheme 60). Meanwhile, only traces of the phenylated pyrroloindolone **98ch** resulted from coupling with a phenyl group in **26q** were detected.



Scheme 60: Alkenylation-cyclization cascade reaction.

Finally, the pyrroloindolone **98ah** was treated with $LiAlH_4$, delivering the desired reduction product pyrroloindoline **117ah** in 88% yield (Scheme 65).



Scheme 61: Reduction of pyrroloindolone **98ah** to pyrroloindoline **117ah**.

Overall, although this approach for the pyrroloindolone synthesis required an elevated reaction temperature, it displayed its high efficacy and avoided to use any transition metals. Meanwhile, it was found that a variety of alkyl substituents at the C2 position of the indole was tolerated under these optimized conditions.

3.4 Metal-Free Arylations of Peptide-Containing Indolylacetamides

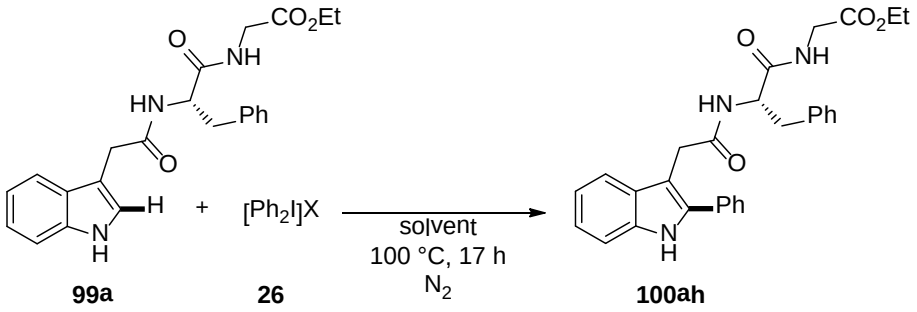
The late-stage functionalization of bioactive small molecules and synthetic biopolymers bears great potential for the direct labeling of specific structural motifs and is, for instance, attractive for the site-selective modification of peptides or proteins.[96–107]

The newly developed efficient methodology for the site-selective metal-free C–H arylation of indoles **95** enabled the straightforward functionalization of more fragile indole substrates, such as peptide-containing indolylacetamides **99**. Through the pre-attachment of an indolylacetyl group to the *N*-terminus of an amino acid or a peptide, the chemo- and site-selective late-stage modification of peptides could be expected, and the use of expensive, toxic and difficult to remove metal catalysts could be avoided.

3.4.1 Optimization Studies

Initial experiments showed the optimal conditions to be highly dependent on the reaction solvent and the counteranion of the diaryliodonium salt **26** (Table 12). The arylation of the dipeptide ethyl [2-(1*H*-indol-3-yl)acetyl-L-phenylalanyl-glycinate (**99a**) with hypervalent iodine(III) compound **26** regioselectively delivered the desired product **100aa**, with best results being accomplished in DMF as the solvent (entries 1–6). Conversely, the corresponding trifluoroacetate ([Ph_2I]TFA) and bromide ([Ph_2I]Br) proved to be ineffective, while the trifluoromethylsulfonate ([Ph_2I]OTf) and the tetrafluoroborate ([Ph_2I]BF_4) gave reduced yields of the desired indole (entries 7–10). Notably, the metal-free C–H bond functionalization of dipeptide **99a** did not require inert reaction conditions, but readily proceeded with a comparable efficiency under an atmosphere of ambient air, again highlighting the robust nature of the user-friendly protocol (entry 11).

Table 12: Optimization of metal-free arylation of dipeptide **99a**.[a]



99a **26** **100ah**

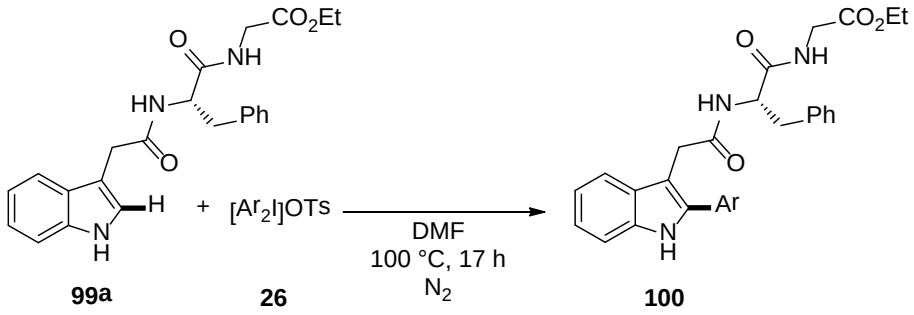
Entry	X	Solvent	Yield [%][b]
1	OTs	DCE	72
2	OTs	toluene	47
3	OTs	1,4-dioxane	11
4	OTs	DMSO	0
5	OTs	*t*AmOH	38
6	**OTs**	**DMF**	**85**, **83**[c]
7	OTf	DMF	42
8	BF_4	DMF	54
9	TFA	DMF	17
10	Br	DMF	0
11	**OTs**	**DMF**	**68**[c,d]

[a] Reaction conditions: **99a** (0.250 mmol), **26** (0.375 mmol), solvent (2.0 mL), 100 °C, 17 h. [b] ^{1}H NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. [c] Yield of the isolated product. [d] Under an atmosphere of ambient air.

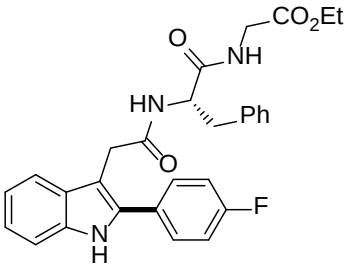
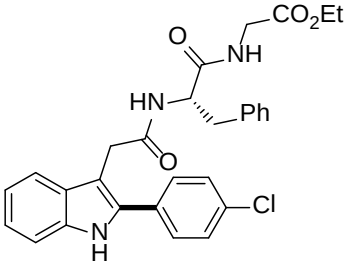
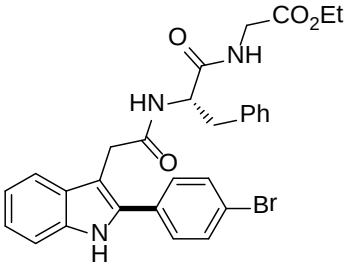
3.4.2 Substrate Scope of Arylation Reactions

In consideration of the importance of applications to the site-specific peptide labeling, we next tested the versatility of the optimized reaction conditions for the direct C–H bond functionalization of the dipeptide **99a** with variously substituted diaryliodonium tosylates **26** (Table 13). Notably, a variety of arylating agents was found to be suitable partners in this metal-free C–H bond arylation reaction. Meanwhile, the halogen-containing motifs were also well tolerated (entries 1–3). Electron-rich hypervalent iodine(III) compounds afforded the C2-arylated products **100al** and **100ag** in excellent yields (entries 4 and 5). Not surprisingly, the sterically demanding arylating reagent **26m** lowered the arylation efficacy (entry 6).

Table 13: Metal-free C–H arylations of dipeptide **99a**.[a]

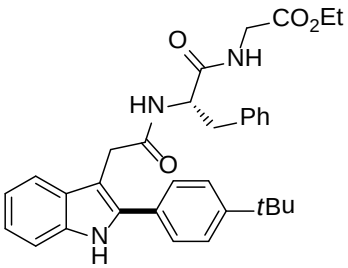
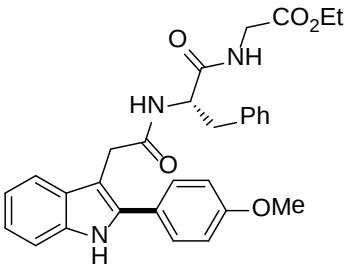
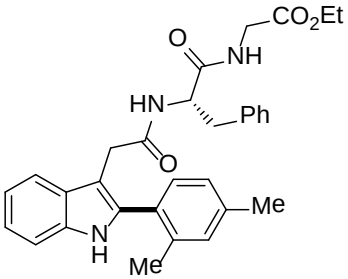


99a **26** **100**

Entry	Ar	Product	Yield [%]
1	4-FC_6H_4 **26i**	 **100abi**	71
2	4-ClC_6H_4 **26j**	 **100aj**	63
3	4-BrC_6H_4 **26k**	 **100ak**	61

(continued)

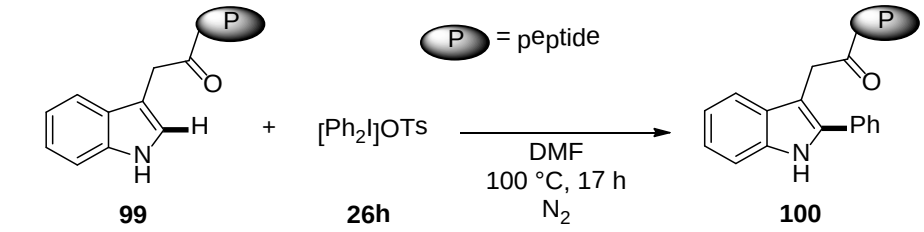
(continued)

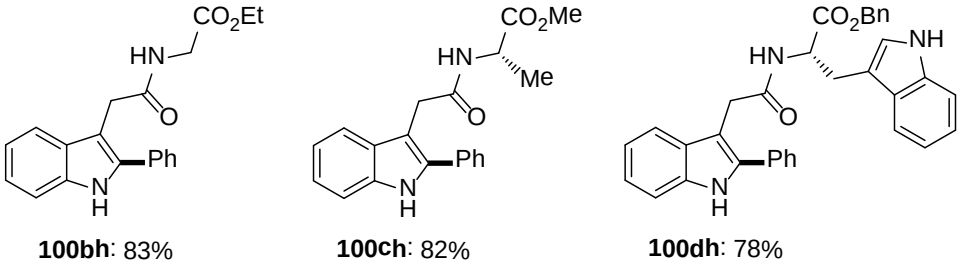
Entry	Ar	Product	Yield [%]
4	4-*t*BuC$_6$H$_4$ **26l**	 **100al**	87
5	4-MeOC$_6$H$_4$ **26g**	 **100ag**	75
6	2,4-Me$_2$C$_6$H$_3$ **26m**	 **100am**	39

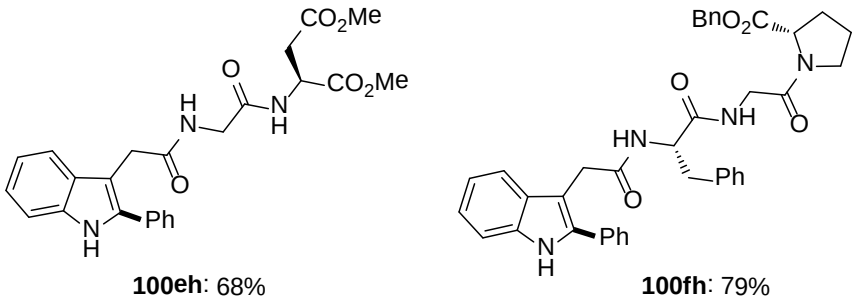
[a] Reaction conditions: **99a** (0.250 mmol), **26** (0.375 mmol), DMF (2.0 mL), 100 °C, 17 h; yield of the isolated product.

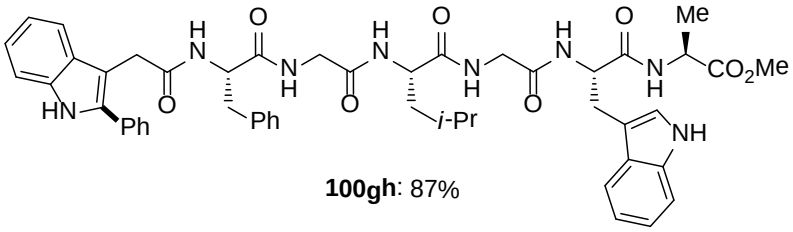
Subsequently, we turned our attention to the desired late-stage diversification of enantiomerically pure peptides **99** (Scheme 62). Several peptides derived from various amino acids were functionalized exclusively at the C2 position of the indole moiety in moderate to excellent yields. The protocol proved to be tolerant of valuable functionalities. Most notably, the arylation of tryptophan-containing substrates **99d** and **99g** displayed an outstanding chemoselectivity, in that the arylation only took place at the indole-3-acetamide moiety rather than the indole in the tryptophan fragment. Intriguingly, this metal-free arylation strategy was also well compatible with a more complicated hexapeptide **99g** without any decrease in reactivity. Notably, under these reaction conditions, no noticeable racemization of peptides

was observed during the C–H arylation.[122]







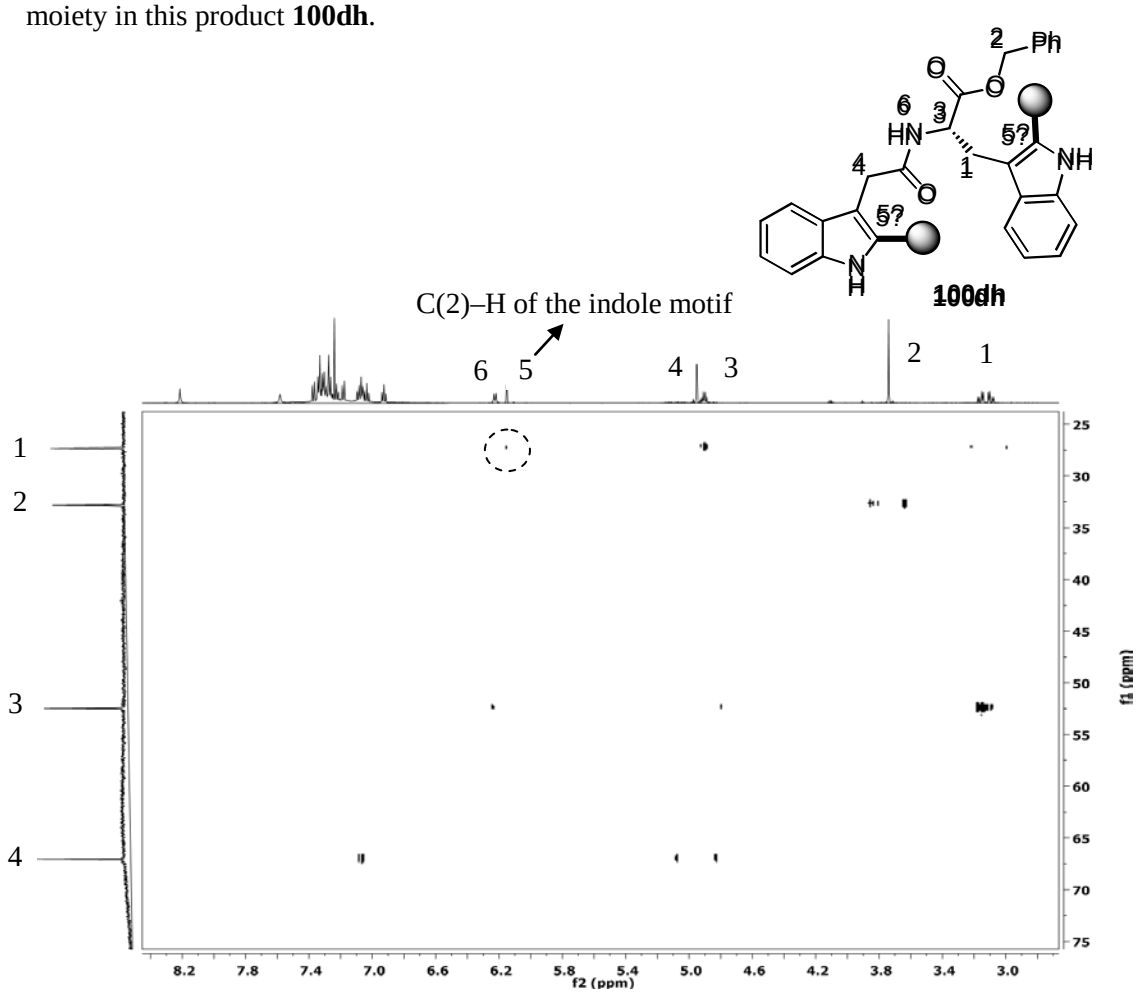


Scheme 62: Metal-free C–H arylations of peptides **99**.

In order to confirm the site-selectivity in the arylation of the tryptophan-containing peptide **99**, a 2D-HMBC spectrum of the arylated product **100dh** was measured in $CDCl_3$. As shown in Scheme 63, the first peak at 27 ppm in ^{13}C-NMR sprectrum (marked with a number 1) accounts for the carbon of methylene group in tryptophan. It interacts with a proton at 6.2 ppm (marked with a number 5), which is assigned to the C(2)–H of the indole motif. Thus, it

[122] For the exploration of racemization-prone peptides, see: J. Ploog, *Master thesis*, Universität Göttingen, **2013**.

can be concluded that the aryl group substituted at the C2 position of the indoleacetamide moiety in this product **100dh**.



Scheme 63: 2D-HMBC spectrum of arylated product **100dh** (measured in $CDCl_3$).

3.5 Palladium-Catalyzed Direct Arylations of Tryptophan-Containing Peptides

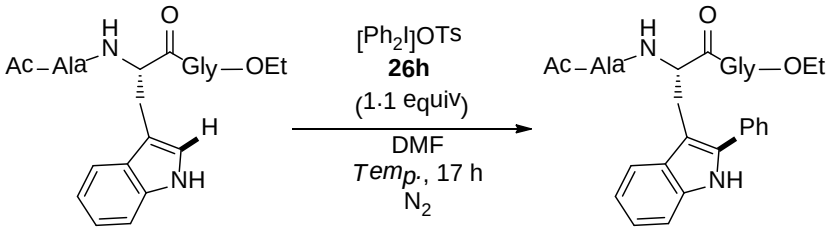
Due to the bioactivities and structural diversity, peptides consisting of natural α-amino acids or of non-proteinogenic amino acids find major applications in the pharmaceutical industry and catalytic asymmetric reactions.[94,95]

In order to conveniently obtain a range of modified tryptophan-containing peptides, *Lavilla*[104] and *Fairlamb*[105] successively developed two methods to realize palladium-catalyzed arylations of tryptophans in moderate to good yields. To obtain high productivity of these catalytic reactions, however, the catalyst loading and the amount of arylating reagents as well as of oxidant must be rather high. Moreover, these reactions proceeded mostly at elevated reaction temperature.

Within our research program on the modification of indoles and the application onto bioactive peptides, we set out to develop a convenient and mild protocol for the direct C–H bond arylation of tryptophan-containing peptides **101**.

3.5.1 Optimization Studies

As discussed above in the Chapters 3.4, the peptide-containing indolylacetamides **99** can successfully be arylated in the absence of any transition metal catalysts. Unfortunately, according to the crude ^{1}H NMR spectra, no desired arylated tripeptide **102ah** was obtained, when this usually high yielding protocol was applied to the structurally analogous tryptophan, which was embedded in the tripeptide Ac-Ala-Trp-Gly-OEt **101a**, at either ambient or elevated reaction temperature (Table 14).

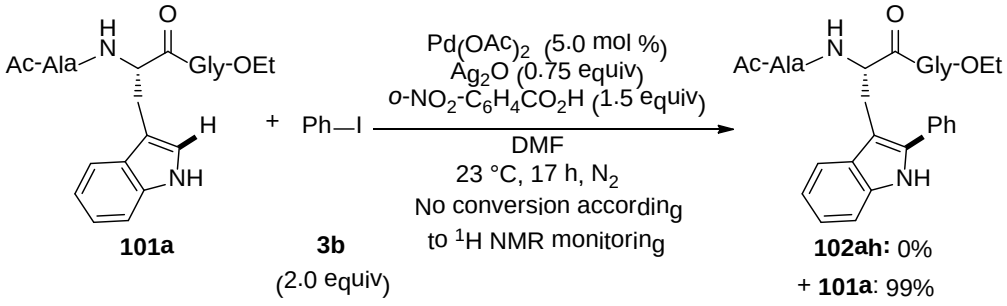


101a **102ah**

Temp. [°C]	Yield [%]
23	0
100	0

Table 14: Attempted metal-free arylation of tryptophan-containing tripeptide **101a**.

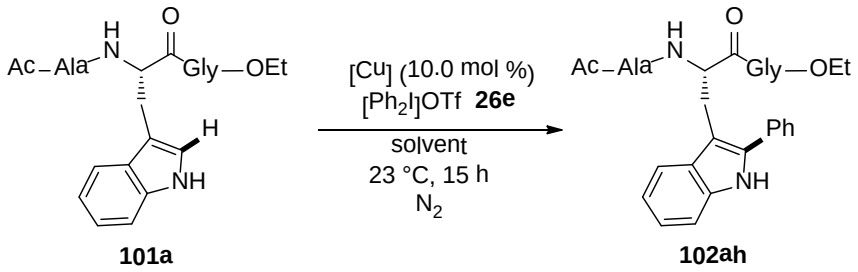
Thereafter, transition metal catalysts were employed to enhance the arylation reactivity. Under *Larrosa*'s reaction conditions, a palladium-catalyzed functionalization of the tryptophan-containing tripeptide **101a** with iodobenzene (**3b**) at ambient temperature was tested. As shown in Scheme 64, the protocol appeared to be inefficient in this particular case. Instead of the desired product **102ah**, only starting material **101a** was reisolated from the reaction mixture in virtually quantitative yield.



Scheme 64: Attempted palladium-catalyzed arylation of the tripeptide **101a** under *Larrosa's* reaction condition.

Besides this, arylation of the tripeptide **101a** was tested in the presence of 10.0 mol % $Cu(OTf)_2$ and diphenyliodonium triflate (**26e**) (Table 15). Among a range of solvents, DCE and CH_2Cl_2 turned out to be partially effective, delivering the arylated tripeptide **102ah** in 12% and 32% yield, respectively (entries 1 and 2). In comparison, other more polar solvents afforded no conversions completely (entries 3–6). Meanwhile, the further screening of copper catalysts gave rise to no significant improvement of the efficiency (entries 7–13). The best reaction conditions exploiting copper(I) chloride as the catalyst yielded **102ah** in only 41% yield (entry 12). The moderate activity of the copper(I)/copper(III) catalytic system is in line with the previously reported conclusion[60a] that the copper catalyst favors C(3)–H bond arylation of indole, in spite of directing effect of substituents on the indole nitrogen atom.

Table 15: Optimization of copper-catalyzed C–H arylation of the tripeptide **101a**.[a]



101a **102ah**

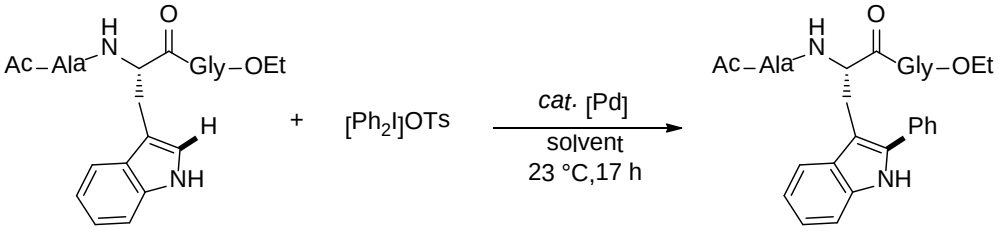
Entry	[Cu]	Solvent	Yield [%][b]
1	$Cu(OTf)_2$	DCE	12
2	$Cu(OTf)_2$	CH_2Cl_2	32
3	$Cu(OTf)_2$	DMF	0
4	$Cu(OTf)_2$	1,4-dioxane	0
5	$Cu(OTf)_2$	MeOH	0
6	$Cu(OTf)_2$	AcOH	0
7	$Cu(OAc)_2$	CH_2Cl_2	30
8	$Cu(OAc)_2 \cdot H_2O$	CH_2Cl_2	18
9	CuOAc	CH_2Cl_2	34
10	CuI	CH_2Cl_2	5
11	$CuBr \cdot Me_2S$	CH_2Cl_2	35
12	CuCl	CH_2Cl_2	41
13	CuCl	CH_2Cl_2/DMF (10/1)	13

[a] Reaction conditions: **101a** (0.20 mmol), **26e** (0.22 mmol), [Cu] (10.0 mol %), solvent (2.0 mL), 23 °C, 15 h. [b] ^{1}H NMR conversion with 1,3,5-trimethoxybenzene as the internal standard.

Fortunately, the reaction yields were considerably improved by replacing copper catalyst by palladium compounds. As shown in Table 16, the reaction solvent played a crucial role in the palladium-catalyzed transformations (entries 1–5). While solvents, such as DMF, toluene or DCE, afforded moderate to good yields, AcOH drove the reaction to an almost quantitative production of the arylated tripeptide **102ah**. The acid CF_3COOH however did not offer any benefit. This significant solvent effect can be rationalized in terms of complexing ability of the acetic acid as a ligand, which is coordinated to the palladium catalyst and thus involved into the catalytic cycle. Notably, the catalyst loading was also important for the

transformation. Thus, loading decrease of $Pd(OAc)_2$ to 0.5 mol % lowered the catalytic competence, delivering **102ah** in 61% yield (entry 6). Moreover, the comparative arylations employing other palladium catalyst sources highlighted the priority of AcOH over other solvents again (entries 7–9).

Table 16: Optimization of palladium-catalyzed C–H arylation of the tripeptide **101a**.[a]



101a **26h** **102ah**

Entry	[Pd]	Solvent	Yield [%]
1	$Pd(OAc)_2$	DMF	59
2	$Pd(OAc)_2$	toluene	66
3	$Pd(OAc)_2$	DCE	85
4	**$Pd(OAc)_2$**	**AcOH**	**99**
5	$Pd(OAc)_2$	CF_3COOH	39
6	$Pd(OAc)_2$	AcOH	61[b]
7	$(MeCN)_2PdCl_2$	AcOH	99
8	$Pd(TFA)_2$	AcOH	99
9	$Pd(TFA)_2$	CF_3COOH	46

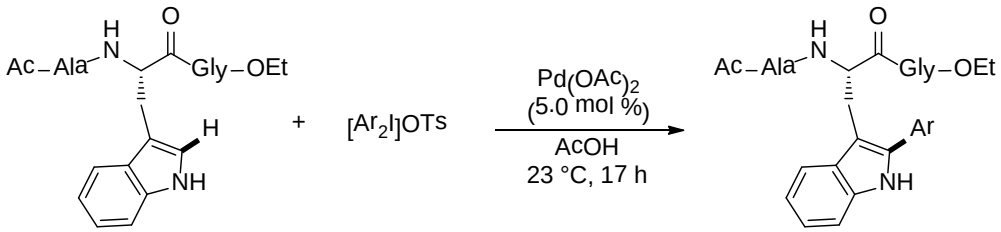
[a] Reaction conditions: **101a** (0.2 mmol), **26h** (0.3 mmol), [Pd] (5.0 mol %) solvent (3.0 mL), 23 °C, 17 h; yield of the isolated product. [b] 0.5 mol % $Pd(OAc)_2$.**3.5.2 Scope of Symmetrical Diaryliodonium Salts**

Encouraged by the efficiency and the high regioselectivity observed in the palladium-catalyzed direct C–H bond arylation of tryptophan-containing tripeptides **101** in AcOH, we examined its generality with respect to symmetrical diaryliodonium tosylates **26** and peptides **101**.

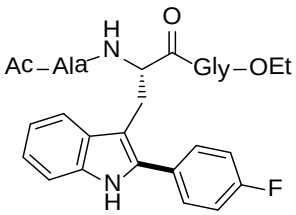
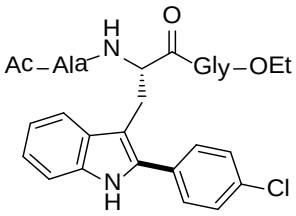
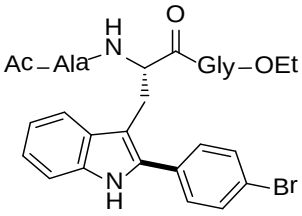
As shown in Table 17, both electron-rich and electron-deficient aryl groups in hypervalent iodine(III) compounds **26** kept the reaction reactivity at a high level, accomplishing the biheteroaryl formation in good to excellent yields (entries 1–4). However, the sterically

demanding aryl groups in **26** were not well tolerated with this approach. Thus, bis(2,4-dimethylphenyl)iodonium tosylate (**26g**) afforded the arylated tripeptide **102am** in only 51% yield (entry 5).

Table 17: Palladium-catalyzed arylations of the tripeptide **101a** with symmetrical λ^3-iodanes **26**.[a]

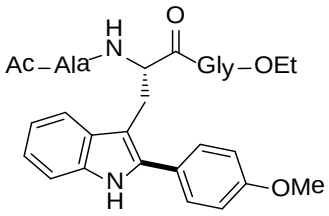
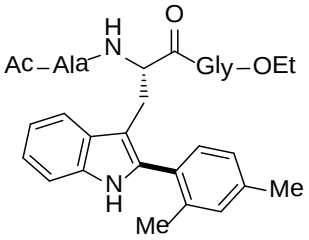


101a **26** **102**

Entry	Ar	Product	Yield [%]
1	4-FC_6H_4 **26i**	 **102ai**	93
2	4-ClC_6H_4 **26j**	 **102aj**	94
3	4-BrC_6H_4 **26k**	 **102ak**	79

(continued)

(continued)

Entry	Ar	Product	Yield [%]
4	4-$MeOC_6H_4$ **26g**	 **102ag**	85
5	2,4-$Me_2C_6H_3$ **26m**	 **102am**	51

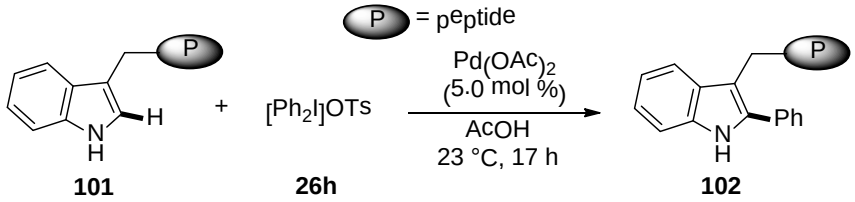
[a] Reaction conditions: **101a** (0.2 mmol), **26** (0.3 mmol), $Pd(OAc)_2$ (5.0 mol %), AcOH (3.0 mL), 23 °C, 17 h; yield of the isolated product.

Thereafter, we explored the versatility of this method by testing several peptide sequences (Table 18). The arylations of the tripeptides **101b** and **101c** afforded the desired products **102bh** and **102ch** in excellent yields (entries 1 and 2). The reaction yield decreased to 56% in the case of the tripeptide Ac-Gly-Trp-Glu$(OMe)_2$ (**101d**) (entry 3). Unfortunately, wenn the sulfur-containing amino acids, such as methionine and cysteine, were embedded in the peptide sequences, the arylations did not proceed (entries 4 and 5). This result could presumably be attributed to the palladium-catalyzed selective hydrolysis of the peptide bond[123] or the formation of the sulfonium salt.[124]

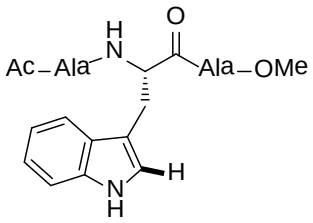
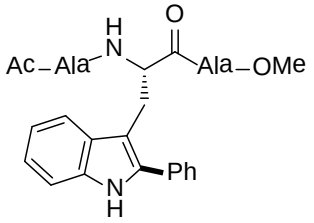
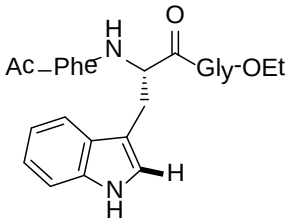
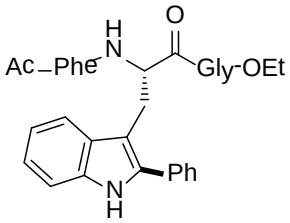
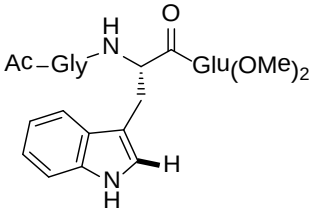
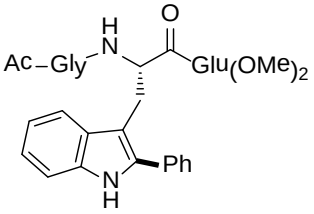
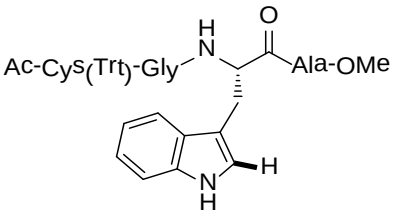
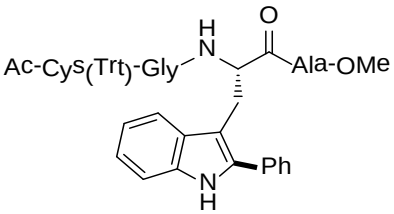
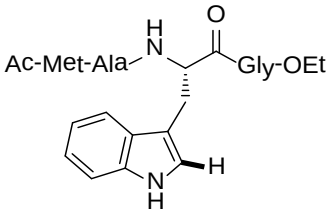
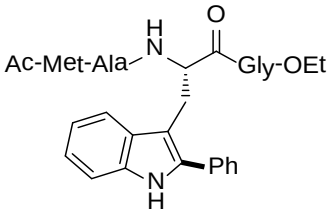
[123] L. Zhu, L. Qin, T. N. Parac, N. M. Kostic, *J. Am. Chem. Soc.* **1994**, *116*, 5218–5224.

[124] (a) J. V. Crivello, J. H. W. Lam, *J. Org. Chem.* **1978**, *43*, 3055–3058; (b). L. Wang, Z.-C. Chen, *Synth. Commun.* **2001**, *31*, 1227–1232; (c) A. Krief, W. Dumont, M. Robert, *Chem. Commun.* **2005**, 2167–2168.

Table 18: Scope of palladium-catalyzed C–H arylation of peptides **101**.[a]



101 **26h** **102**

Entry	Substrate	Product	Yield [%]
1	 **101b**	 **102bh**	98
2	 **101c**	 **102ch**	86
3	 **101d**	 **102dh**	56
4	 **101e**	 **102eh**	0
5	 **101f**	 **102fh**	0

[a] Reaction conditions: **101** (0.2 mmol), **26h** (0.3 mmol), $Pd(OAc)_2$ (5.0 mol %), AcOH (3.0 mL), 23 °C, 17 h; yield of the isolated product.

3.5.3 Scope of Unsymmetrical Diaryliodonium Salts

Unsymmetrical diaryliodonium salts, which are favored due to their potentially improved atom economy and relative ease of preparation, are also potential candidates for site-selective arylations of tryptophan-containing tripeptides. In arylation reactions employing unsymmetrical diaryliodonium salts, the problem of chemoselectivity between two different aryl groups appears inevitably. In order to discriminate one of the two aryl group, the bulky mesityl group can be introduced to the unsymmetrical salt. Under the optimized reaction conditions for the palladium-catalyzed C–H arylation, the sterically less hindered aryl group should be selectively transferred to the nucleophilic indole moiety.

Various unsymmetrical diaryliodonium tosylates **26** bearing the mesityl group were synthesized and tested in the arylation reaction of the tripeptide **101a** in the presence of AcOH. The results are summarized in Table 19. Thus, the (mesityl)(4-methoxyphenyl)-iodonium tosylate (**26r**) afforded the desired tripeptide **102ag** in AcOH in 57% yield (entry 1). A slight modification utilizing a solvent mixture of AcOH and DCE in a ratio of 1:1, where DCE was used to improve the solubility of the unsymmetrical diaryliodonium salts **26**, slightly meliorated the reaction yield to 64% (entry 2). However, in comparison with the reaction of symmetrical bis(4-methoxyphenyl)iodonium tosylate (**26g**) (Table 9, entry 4), the reactivity was remarkably lowered, presumably due to the steric hindrance with the bulky diaryliodonium salt.

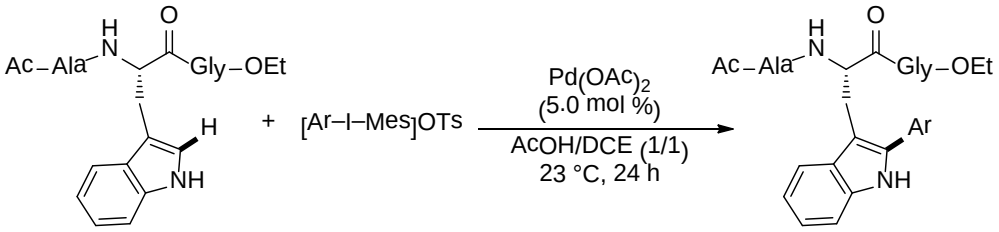
The electron-rich aryl groups of λ^3-iodane **26** were easier transferred to the indole moiety of **101a** under the palladium catalysis than the electron-deficient aryl groups. Thus, whereas the (mesityl)(4-tolyl)iodonium tosylate (**26s**) provided the arylated tripeptide **102as** in a moderate yield of 55% (entry 3), the desired product **102at** was obtained employing (mesityl)(3-trifluorophenyl)iodonium tosylates (**26t**) in only 33% yield (entry 4).

On the other hand, the (mesityl)(1-naphthalenyl)iodonium tosylate (**26u**) was well tolerated under these reaction conditions, delivering the arylated tripeptide **102au** in 70% yield

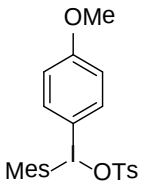
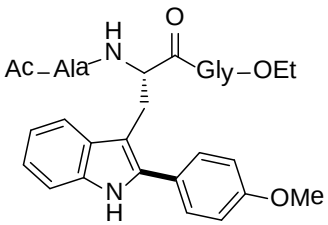
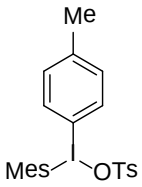
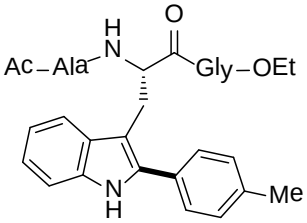
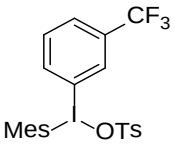
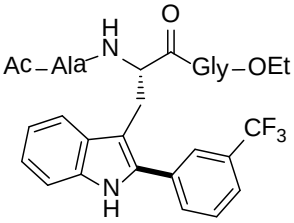
(entry 5).

Interestingly, unsymmetrical iodonium tosylates **26v** and **26w** bearing amino acid moieties became viable substrates as well (entries 6 and 7). These phenylalanine- and glycine-derived λ^3-iodanes gave rise to new peptides **102av** and **102aw** in 53% and 36% yield, respectively. These reactions displayed a potential for the ligation of two non-natural peptides.

Table 19: Arylation of the tripeptide **101a** with unsymmetrical diaryliodonium tosylates **26**.[a]

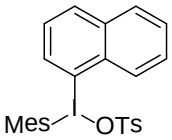
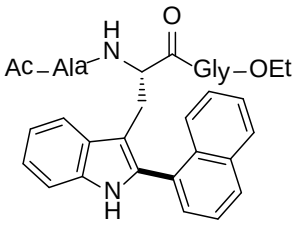
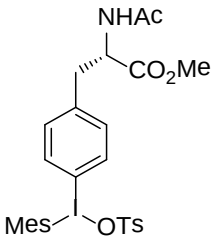
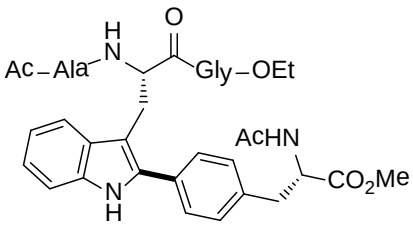
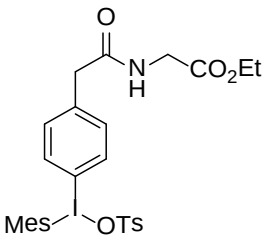
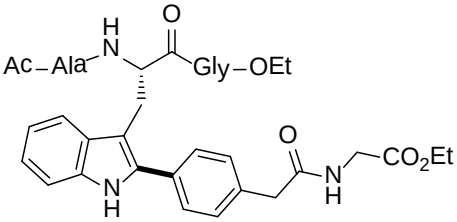


101a **26** **102**

Entry	[Ar-I-Mes]OTs	Product	Yield [%]
1	 **26r**	 **102ag**	57[b]
2			64
3	 **26s**	 **102as**	55
4	 **26t**	 **102at**	33

(continued)

(continued)

Entry	[Ar-I-Mes]OTs	Product	Yield [%]
5	 **26u**	 **102au**	70
6	 **26v**	 **102av**	53
7	 **26w**	 **102aw**	36

[a] Reaction conditions: **101a** (0.2 mmol), **26** (0.3 mmol), $Pd(OAc)_2$ (5.0 mol %), AcOH (1.5 mL), DCE (1.5 mL), 23 °C, 24 h; yield of the isolated product. [b] AcOH (3.0 mL) as the solvent.

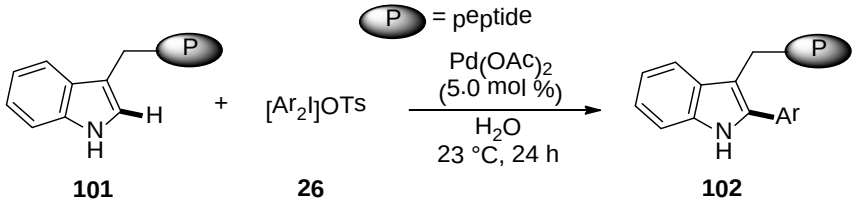
3.5.4 Water as the Reaction Medium

Given that a wide range of *in vivo* syntheses of biological substrates, such as peptides, are carried out under aqueous conditions, water as an inexpensive, environmentally benign, nontoxic reaction medium has been gradually utilized to perform *in vitro* organic reactions.[125] Hence, the above developed palladium-catalyzed C–H bond functionalization was further explored employing water as the reaction medium (Table 12). Differing from organic solvents, water has a low dissolving capacity of organic compounds, such as the tripeptide **101** and the diaryliodonium tosylate (**26**).

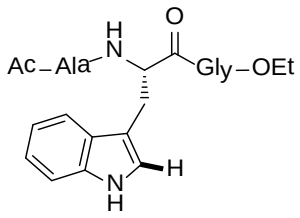
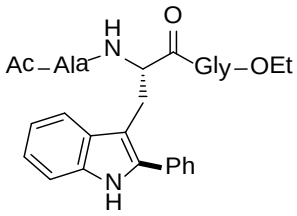
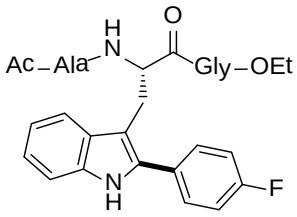
[125] (a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; (b) A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725–748; (c) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302–6337.

After a simple replacement of organic solvent with water, the reaction of the tripeptide **101a** Ac-Ala-Trp-Gly-OEt with the diphenyliodonium tosylate (**26h**) afforded a satisfactory outcome with 70% yield (entry 1). Further exploration of other arylating reagents **26** showed good performance as well (entries 2–8). We were surprised to find that the sterically demanding 2,4-dimethylphenyl group afforded the arylated peptide **102am**, which under acidic conditions was previously obtained in only 51% yield (Table 17, entry 5), in high yield of 71% (entry 8). Whereas the arylation reaction of **101b** Ac-Ala-Trp-Ala-OMe with the aqueous medium still afforded the product **102bh** with moderate efficacy (54% yield, entry 9), the arylated tripeptides **102dh** can be synthesized from substrate Ac-Gly-Trp-Glu(OMe)$_2$ **102d** in only 23% yield (entry 10).

Table 20: Palladium-catalyzed C–H arylation with H_2O as the reaction medium.[a]

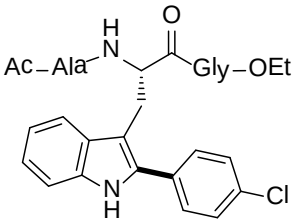
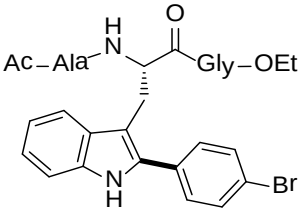
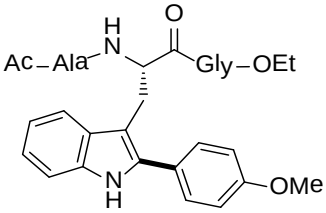
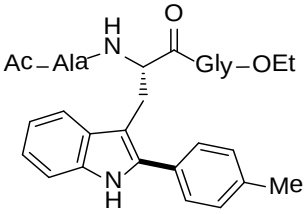
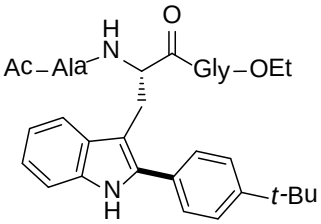


101 **26** **102**

Entry	Substrate	Ar	Product	Yield [%]
1	 **101a**	Ph **26h**	 **102ah**	70
2	**101a**	4-FC_6H_4 **26i**	 **102ai**	95

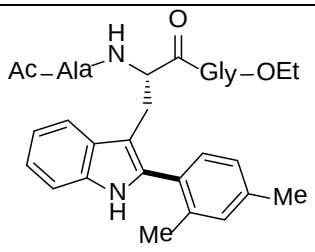
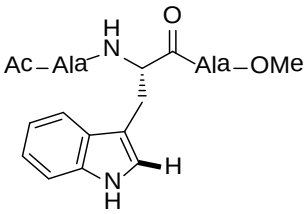
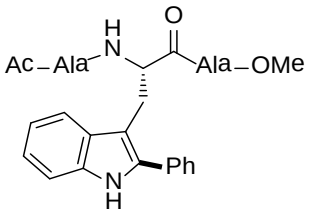
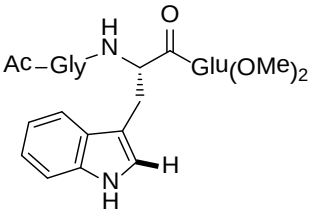
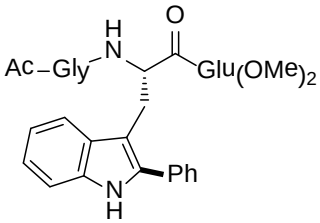
(continued)

(continued)

Entry	Substrate	Ar	Product	Yield [%]
3	**101a**	4-ClC_6H_4 **26j**	 **102aj**	64
4	**101a**	4-BrC_6H_4 **26k**	 **102ak**	54
5	**101a**	4-$MeOC_6H_4$ **26g**	 **102ag**	80
6	**101a**	4-MeC_6H_4 **26x**	 **102as**	61
7	**101a**	4-*t*BuC_6H_4 **26l**	 **102al**	77

(continued)

(continued)

Entry	Substrate	Ar	Product	Yield [%]
8	**101a**	2,4-$Me_2C_6H_3$ **26m**	 **102am**	71
9	 **101b**	Ph **26h**	 **102bh**	54
10	 **101d**	Ph **26h**	 **102dh**	23

[a] Reaction conditions: **101** (0.2 mmol), **26** (0.3 mmol), $Pd(OAc)_2$ (5.0 mol %), H_2O (3.0 mL), 23 °C, 24 h; yield of the isolated product.

Furthermore, the unsymmetrical (mesityl)(4-methoxyphenyl)iodonium tosylate (**26r**) was also employed to test its reactivity with water as the reaction medium (Table 21). Unfortunately, the optimized reaction conditions appeared to be less effective for arylations with unsymmetrical diaryliodonium tosylates **26r**.

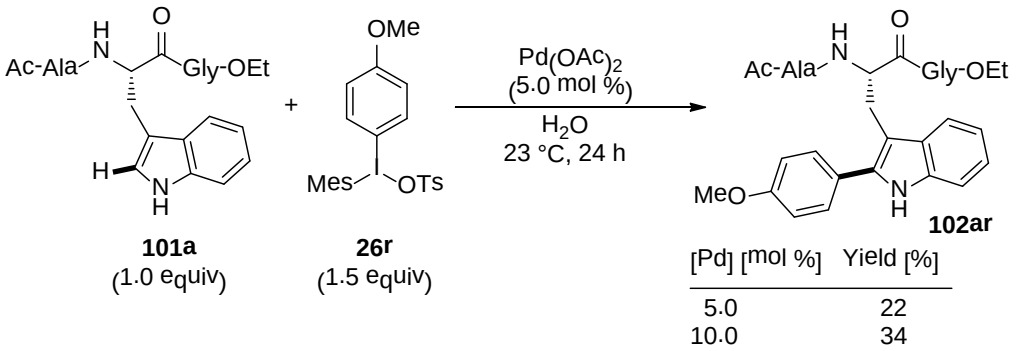
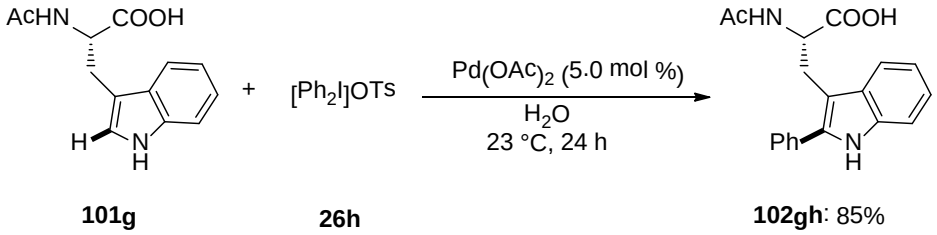


Table 21: Palladium-catalyzed C–H arylation with **26r** with H_2O as the reaction medium.

To test the reaction potential of peptides bearing a free *C*-terminus, a simple acetylated tryptophan Ac-Trp-OH **101g** was subjected to the catalytic arylation. When the symmetrical diphenyliodonium tosylate **26h** was the arylating partner, 85% of the phenylated product **102gh** was obtained (Scheme 65).

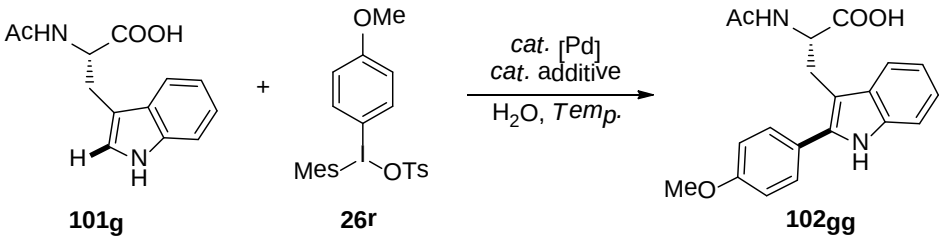


101g **26h** **102gh**: 85%

Scheme 65: Arylation of amino acid **101g** with diphenyliodonium tosylate **26h**.

However, the unsymmetrical hypervalent iodine(III) compound **26r** did not demonstrate the same high reactivity (Table 22). Under the typical reaction conditions, the arylated tryptophan **102gg** was obtained in only 39% yield (entry 1). Elevated temperature had a minor effect on the outcome (entry 2). Taking into consideration the capability of surfactants to improve reactions with water,[126] the surfactant PTS (polyoxyethanyl α-tocopherylsebacate) was examined as the additive (entry 3). Unfortunately, the reaction in the presence of a catalytic amount of the surfactant PTS did not provide improved yield in this case. Moreover, a palladium catalyst containing a water-soluble ligand guanidine also turned out to be inefficient for this biaryl synthesis (entry 4).[127]

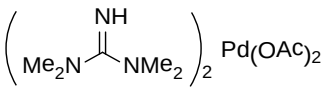
Table 22: Arylation of Ac-Trp-OH **101g** with unsymmetrical hypervalent iodine(III) **26r**.[a]



101g **26r** **102gg**

[126] (a) B. H. Lipshutz, B. R. Taft, *Org. Lett.* **2008**, *10*, 1329–1332; (b) B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.* **2008**, *10*, 1333–1336.

[127] (a) Z. Gao, V. Gouverneur, B. G. Davis, *J. Am. Chem. Soc.* **2013**, *135*, 13612–13615; (b) A. Dumas, C. D. Spicer, Z. Gao, T. Takehana, Y. A. Lin, T. Yasukohchi, B. G. Davis, *Angew. Chem. Int. Ed.* **2013**, *52*, 3916–3921.

Entry	[Pd]	Additive	Yield [%][b]
1	$Pd(OAc)_2$	---	39
2	$Pd(OAc)_2$	---	40[c]
3	$Pd(OAc)_2$	PTS	29
4		---	12

[a] Reaction conditions: **101g** (0.2 mmol), **26r** (0.3 mmol), [Pd] (5.0 mol %), additive (3.0 wt %), H_2O (3.0 mL), 23 °C, 24 h. [b] ^1H NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. [c] Reaction temperature of 37 °C.

Overall, our results demonstrate that water is a very promising reaction medium for palladium-catalyzed C–H arylations of tryptophan-containing peptides **101**. Compared to reactions under acidic conditions, however, transformations in the aqueous medium remain challenging, especially the reactions of sterically demanding substrates.

3.5.5 UV-Vis and Fluorescence Studies

The optical properties (absorption and fluorescence maxima, stoke shift and molar absorptivity) for the peptides **101a**, **102ag–am** and **102as–aw** are presented in Table 23. All of these peptides showed an intense absorption band in the UV region (see Chapter 5.4.6). With the exception of the bromophenylated tripeptide **102ak**, these chromophores were also fluorescent in the UV-Vis region. Moreover, the arylated peptides **102** exhibited a red-shifted absorption/emission wavelength relative to the free tripeptide **101a**.

By comparing the arylated peptides **102ag–am**, **102as–at** and **102av–aw**, it could be apparently found that both electron-donating and electron-withdrawing groups at the *meta*- or *para*-position of the phenyl rings could affect the optical properties. Notably, the 3-CF_3 group in the peptide **102at** shifted the the absorption and fluorescence maxima from 308 nm for **102ah** to 312 nm in absorption and from 379 nm for **102ah** to 416 nm in emission. Furthermore, the largest Stockes shift was generated, when the naphthalyl group in **102au** substituted at the C2 position of the indole moiety.

The arylated peptide with an electron-donating group generally displayed high fluorescence intensity (Figure 6). Among the arylated peptides, the largest fluorescence intensity was seen

for **102al**. Notably, the heavy atom which could enhance spin-orbit coupling in the molecule can strongly decrease the fluorescence intensity,[128] so that the peptide **102aj** with a chloro group was weakly emissive and **102ak** with a bromo group even non-fluorescent.

Table 23: UV-Vis data and Stokes shifts for the tripeptide **101a** and the arylated tripeptides **102ag–an**, **102hs–hw**.[a]

Compound	Abs. λ_{max} [nm]	Em. λ_{max} [nm]	Stokes shift [nm]	ε [$dm^3 \cdot mol^{-1} \cdot cm^{-1}$]
101a	283	343	60	7036
102ag	310	370	60	23505
102ah	308	379	71	17408
102ai	305	379	74	17027
102aj	313	393	80	20028
102ak	315	-	-	22414
102al	311	376	65	24701
102am	295	377	82	18447
102as	310	379	69	21822
102at	312	416	104	22515
102au	282	451	169	15798
102av	311	380	69	19967
102aw	310	380	70	13361

[a] Solutions of peptides **101a**, **102ag–am** and **102as–aw** in DMSO.

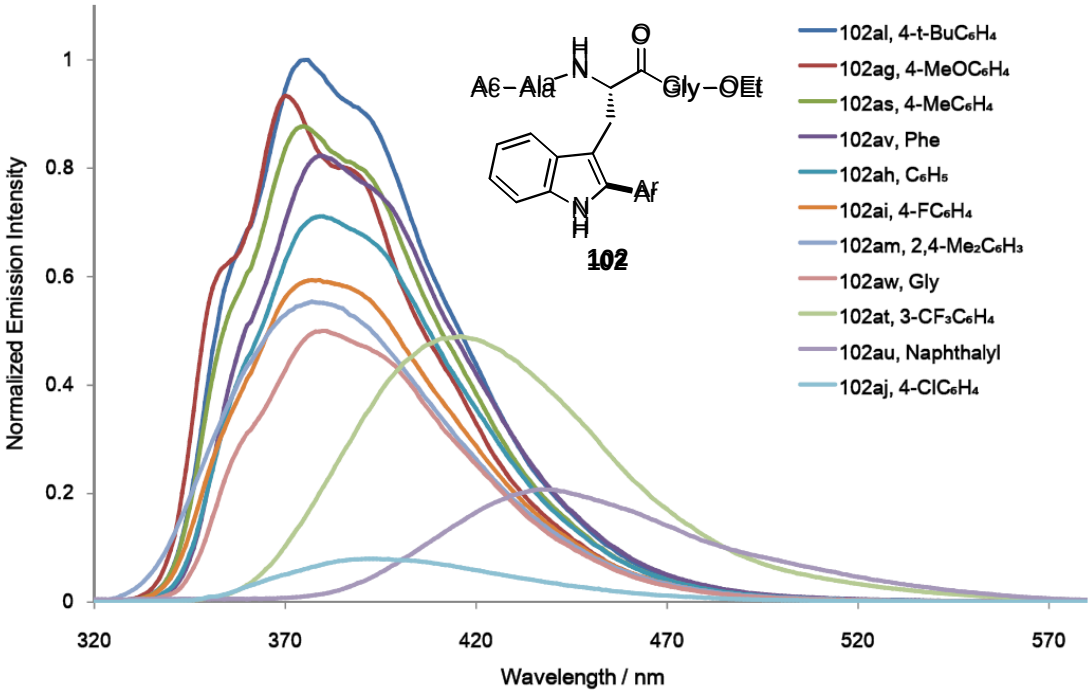


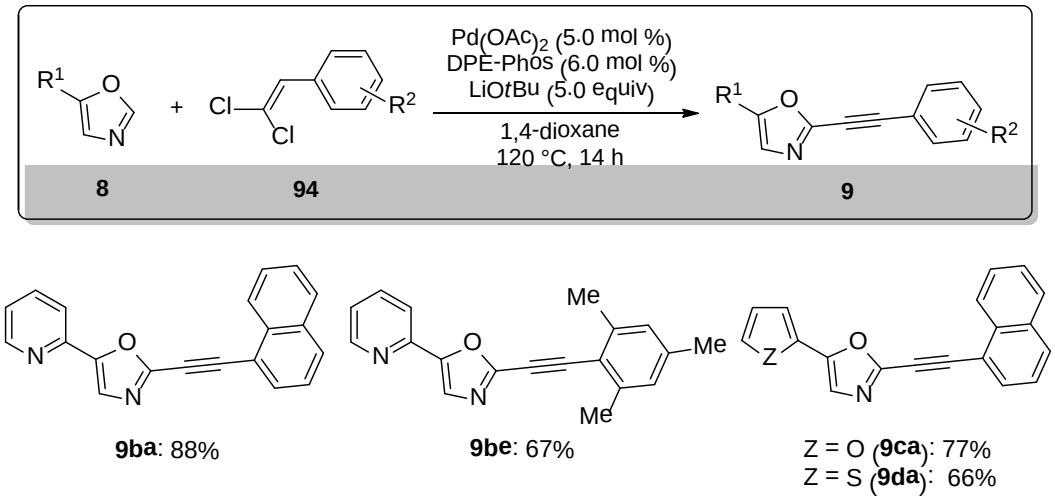
Figure 6: Fluorescence spectra for arylated tripeptides.

[128] D. S. McClure, *J. Chem. Phys.* **1949**, *17*, 905–913.

4 Summary and Outlook

The development of sustainable strategies for the synthesis of highly functionalized *N*-containing heterocycles is of great importance for the preparation of pharmaceuticals, agrochemicals and functional materials. Thus, the focus of the present work was set on the construction of a variety of heterocyclic frameworks through palladium-catalyzed or metal-free direct C−H functionalizations.

In the first project, the substrate scope for the direct C–H bond alkynylation of oxazoles with *gem*-dichloroalkenes employing the catalytic system consisted of $Pd(OAc)_2$, DPE-Phos and LiO*t*Bu was explored (Scheme 66). Pyridyl, thienyl and furyl groups at the C5 position of oxazoles **8b**−**c** were well tolerated. Furthermore, a variety of *gem*-dichloroalkenes **94** bearing polycyclic or sterically bulky arenes proved to be suitable substrates, hereby delivering unsymmetrical acetylenes.

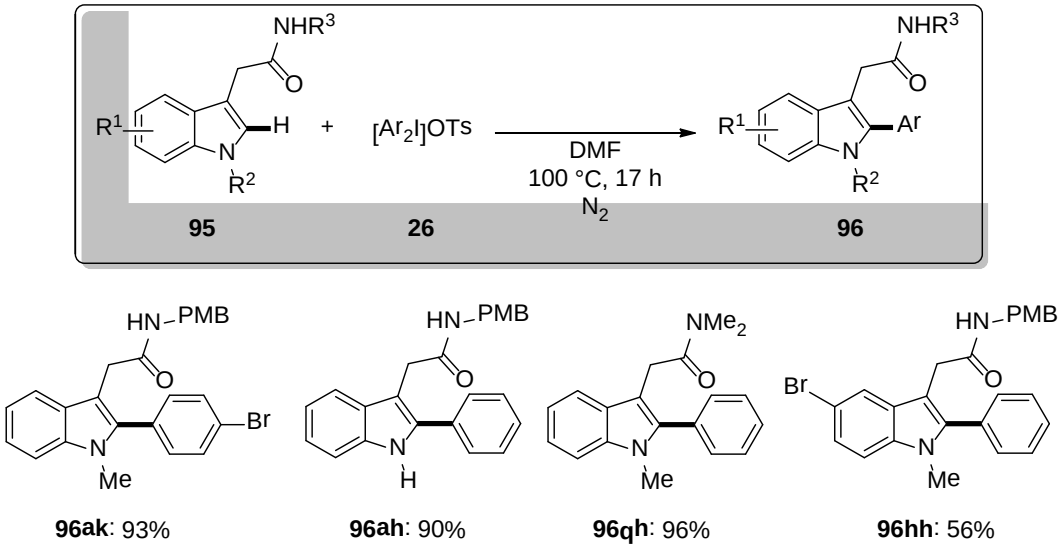


Scheme 66: Palladium-catalyzed alkynylation of oxazoles **8** with *gem*-dichloroalkenes **94**.

In recent decades, diaryliodonium salts **26** have emerged as a potent alternative to haloarenes as arylating reagents. The utilization of diaryliodonium salts allows C–H arylations of (hetero)arenes to take place at low reaction temperatures under transition metal catalysis or even in the absence of the transition metal catalyst.

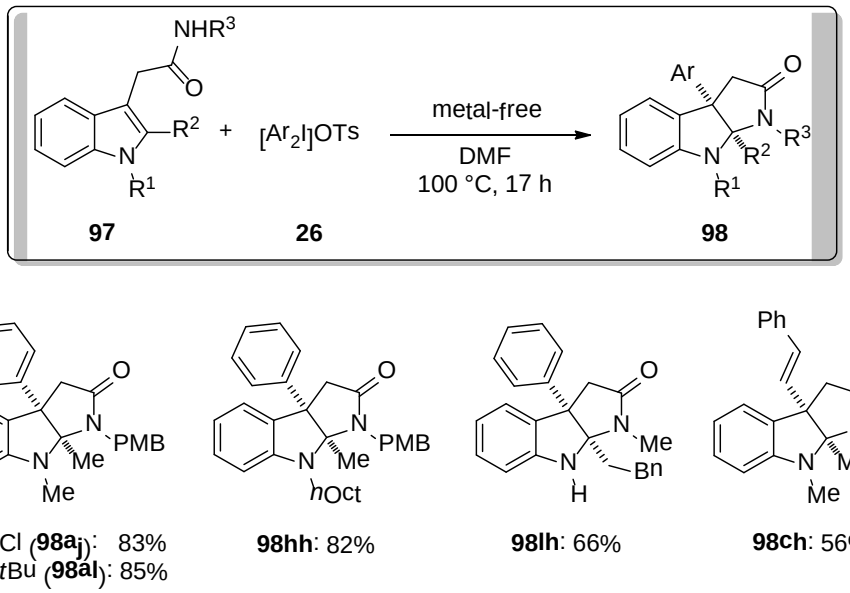
In the second project of this thesis, diaryliodonium tosylates **26** were used for metal-free C2-arylations of indoles **95** bearing the acetamide functionality at the C3 position (Scheme 67). The reaction conditions showed good tolerance of electron-rich and electron-deficient

diaryliodonium salts. Mechanistic studies were indicative of a S_EAr-type functionalization with a subsequent C3→C2 migration.



Scheme 67: Metal-free arylation of indolylacetamides **95**.

Subsequently, the challenging metal-free arylation-cyclization cascade reaction was elaborated by blocking the C2 position of indoles (Scheme 68). A wide range of C2-alkyl rests was found to be viable for the assembly of pyrroloindolones. We were delighted to observe that the cascade reaction also smoothly proceeded with the utilization of (aryl)(alkenyl)iodonium tosylates (**26q**), delivering the C3-styryl pyrroloindoline (**98ch**).

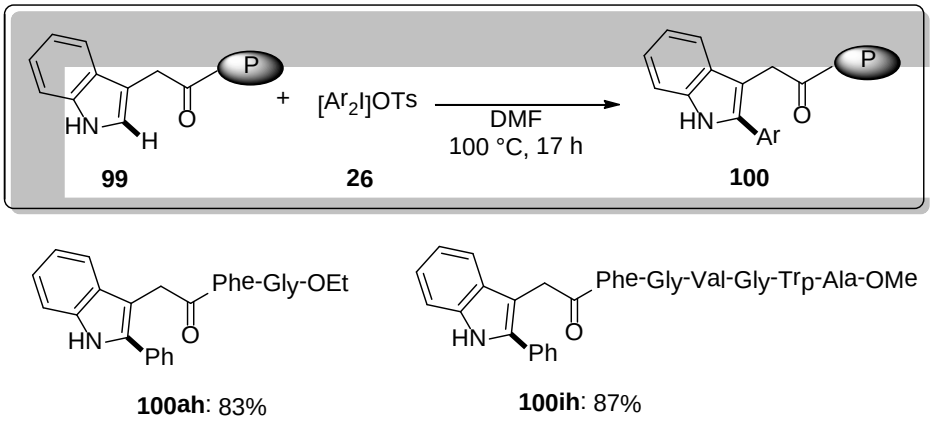


Scheme 68: Metal-free arylation-cyclization cascade reactions.

Prospective endeavours for the metal-free arylation-cyclization cascade reactions could be

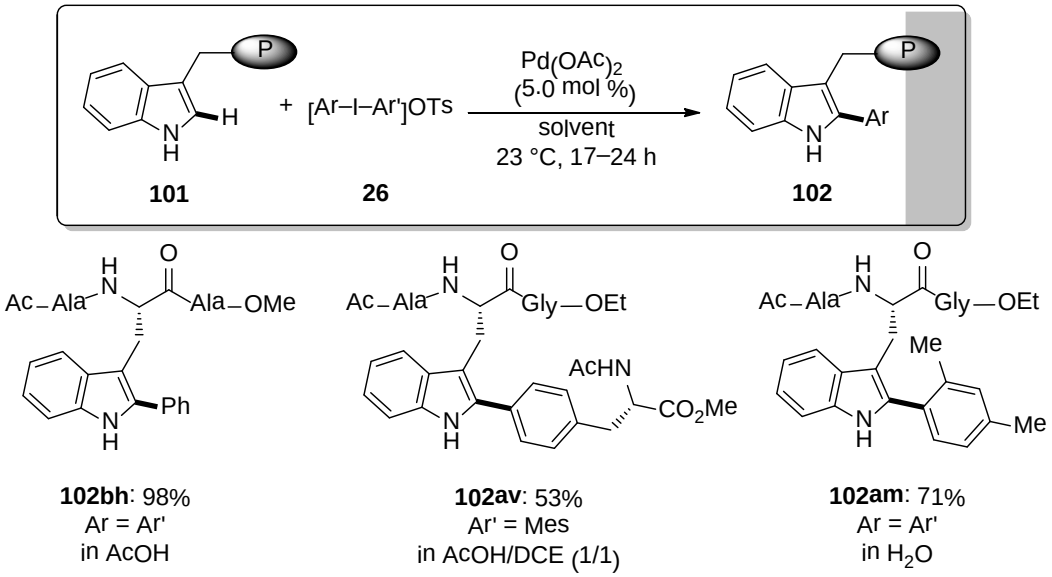
directed towards the employment of a chiral diaryliodonium salt or a suitable chiral catalyst, such as the chiral phosphoric acid **74**, to achieve enantioselective formations of pyrroloindolones.

The last two projects were focused on the late-stage diversification of peptides through the site-selective C−H arylation. The approach for the metal-free C−H arylations was further applied to the peptide **99** involving the indolylacetyl group as a tag. The more complicated substrates, including di-, tri- and even hexapeptides, were capable to furnish the arylated peptides **100** chemo- and site-selectively (Scheme 69). Interestingly, the arylation substrates with two indolyl moieties, one of which was part of a tryptophan residue, took only place at the indole-3-acetamide moiety rather than the tryptophan motif.



Scheme 69: Metal-free late-stage arylations of peptide-containing indolylacetamides **99**.

The post-synthetic modification of the tryptophan-containing peptides **101** was accomplished through the palladium-catalyzed C–H arylation (Scheme 70). The arylation of tripeptides **101** proceeded at ambient temperature by utilizing symmetrical or unsymmetrical diaryliodonium salts **26** as the arylating reagents, respectively. With water as an environmentally benign reaction medium, the arylation reactions still displayed satisfactory performances. Importantly, the amino acid tryptophan with free *C*-terminus proved to be a viable substrate for this chemical transformation.



Scheme 70: Palladium-catalyzed arylations of tryptophan-containing peptides **101**.

Future development of the palladium-catalyzed C–H arylations of tripeptides should be focused on testing the robustness of these reaction conditions by extending substrate scope to include peptides containing different amino acids. And the introduction of a fluorescent aryl group, such as pyrene and BODIPY, to the tryptophan-containing peptide, seems to be promising.

5 Experimental Section

5.1 General Remarks

Unless otherwise noticed, all reactions were carried out under a N_2 atmosphere using pre-dried glassware and standard Schlenk techniques. As to metal-free reactions, new glassware and new stirring bars were used for all reactions.

5.1.1 Solvents

The anhydrous solvents for reactions with moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to the following standard procedures:

***tert*-Amyl alcohol** was stirred over Na for 5 h at 120 °C and distilled under ambient pressure.

1,2-Dichloroethane or ***N*,*N*-dimethylformamide** were stirred with CaH_2 for 8 h, degassed and distilled under reduced pressure.

Dichloromethane was purified using a M. Braun SPS-800 solvent purification system and was stored over molecular sieves.

Dimethyl sulfoxide was stirred with CaH_2 for 4 h, degassed and distilled under reduced pressure.

Methanol was stirred over MgOMe for 3 h at 65 °C prior to distillation.

***N*-Methyl-2-pyrrolidone** was stirred for 4 h at 150 °C and subsequently distilled under reduced pressure.

1,4-Dioxane was dried and distilled over Na/benzophenone ketyl.

Toluene was pre-dried over KH and distilled over Na/benzophenone ketyl.

Water was degassed for 2 h and ultrasonicated.

Acetic acid was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure.

5.1.2 Vacuum

Following pressures were measured on the used vacuum pump and are not corrected: membrane pump vacuum (MPV): 5.0 mbar, oil pump vacuum (OPV): 0.1 mbar.

5.1.3 Chromatography

Analytical TLC was performed on 0.25 mm silica gel 60F plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under ultraviolet light and developed by treatment with a $KMnO_4$ solution or an acidic Cer(IV)-solution followed by careful warming with a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm, 70–230 mesh ASTM).

5.1.4 High-Performance Liquid Chromatography (HPLC)

Preparative separations were performed on an HPLC-System from KNAUER (Smartline Pump 100, Dynamic Mixing Chamber, Injection- and Control-Valve, Smartline UV Detector 2500). Separation column VP C18 ec (RP) (250 × 16 mm, *Nucleodur*, 100-10) from MACHEREY-NAGEL was used. Organic solvents of HPLC-grade and twice distilled H_2O were employed. All samples were filtrated through Polytetrafluorethylen-(PTFE) -Filter from ROTH (Ø 25 mm, 0.2 µm), respectively VWR (Ø 13 mm, 0.2 µm) prior to separation.

5.1.5 Gas Chromatography (GC)

Monitoring of reaction processes *via* coupled gas chromatography-mass spectrometry was performed using *G1800C GCD plus* with mass detector *HP 5971*, *5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from AGILENT TECHNOLOGIES. *HP-5MS* columns (30 m × 0.25 mm, film 0.25 µm) were used.

5.1.6 Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectroscopy was performed at 300 or 600 MHz (^{1}H NMR), 75 or 125 MHz (^{13}C NMR, APT) and 283 MHz (^{19}F NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak.

	^{1}H NMR	^{13}C NMR
$CDCl_3$	7.26 ppm	77.0 ppm
d_6-DMSO	2.49 ppm	49.5 ppm

For characterization of the observed resonance multiplicities the following abbrevations were applied: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublet), *dt* (doublet of triplet), or analogue representations. The coupling constants *J* are reported in Hertz (Hz).

5.1.7 Infrared Spectroscopy (IR)

Infrared spectra were recorded on a BRUKER *Alpha-P* ATR-spectrometer. Liquid probes were measured as film and solid probes neat. Analysis of the spectral data was performed using the *OPUS 3.1* software from BRUKER, respectively *OPUS 6*. Absorption ($\tilde{\nu}$) is given in wave numbers (cm^{-1}). Spectra were recorded in the range of 4000 to 400 cm^{-1}.

5.1.8 Mass Spectroscopy (MS)

EI- and EI-HRMS spectra were measured on a *Time-of-Flight* mass spectrometer *AccuTOF* from JOEL. ESI-mass spectra were recorded on an *Ion-Trap* mass spectrometer *LCQ* from FINNIGAN or on a *Time-of-Flight* mass spectrometer *microTOF* from BRUKER. ESI-HRMS spectra were recorded on a BRUKER APEX IV or a BRUKER DALTONIC (7T, Transform Ion Cyclotron Resonance (FTICR)) mass spectrometer. The ratios of mass to charge are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

5.1.9 Melting Points

Melting points were measured using a Stuart® Melting Point Apparatus SMP3 from BARLOWORLD SCIENTIFIC or BÜCHI 540 Melting Point Apparatus. Reported values are uncorrected.

5.1.10 UV-Visible Spectroscopy

UV-Visible Spectroscopy was performed on a Jasco® V-770 spectrophotometer. A baseline in the appropriate solvent was obtained prior to recording spectra.

5.1.11 Fluorescence Spectroscopy

Fluorescence excitation and emission data in solution were recorded on a Jasco® FP-8500 spectrofluorometer. The widths of excitation and emission slits were held constant at 2.5 and 5 nm, respectively. The scan speed was adjusted to 200 nm/min.

5.1.12 Reagents

Chemicals obtained from commercial sources (purity > 95%) were used without further purification. 3-Chloroperoxybenzoic acid (*m*CPBA) was purchased from ACROS ORGANICS with a purity of 70–75% (rest: 3-chlorobenzoic acid and water) and was used after drying under vacuum at ambient temperature for 1h (calculated as 81% wt).

5.2 Synthesis of Starting Materials

The following starting materials were synthesized according to previously described methods: Oxazoles **8b–d**,[129] *gem*-dichloroalkenes **94a–m**,[130] indolylacetamides **95a–e**, **95g–j**,[131] **95k–s**, α-substituted indolylacetamides **95t–u**,[132] 2-methylindolylacetamides **97a–i**, 2-alkylindolylacetamides **97j–n**,[133] symmetrical diaryliodonium salts **26g–n**,[134] **26x**,[135] dithienyliodonium tosylate (**26o**),[136] (mesityl)(aryl)iodonium tosylates **26r–w**, (phenyl)(vinyl)iodonium triflate (**26q**),[137] (2-allyloxyphenyl)(mesityl)iodonium tosylate

[129] A. M. van Leusen, B. E. Hoogenboom, H. Siderius, *Tetrahedron Lett.* **1972**, *23*, 2369–2372.
[130] S. G. Newman, C. S. Bryan, D. Perez, M. Lautens, *Synthesis* **2011**, 342–346.
[131] S. Petit, Y. Duroc, V. Larue, C. Giglione, C. Léon, C. Soulama, A. Denis, F. Dardel, T. Meinnel, I. Artaud, *ChemMedChem* **2009**, *4*, 261–275.
[132] (a) Y.-F. Zhu, Z. Guo, T. D. Gross, Y. Gao, P. J. Connors, R. S. Struthers, Q. Xie, F. C. Tucci, G. J. Reinhart, D. Wu, J. Saunders, C. Chen, *J. Med. Chem.* **2003**, *46*, 1769–1772; (b) E. Kiuru, Z. Ahmed, H. Lönnberg, L. Beigelman, M. Ora, *J. Org. Chem.* **2013**, *78*, 950–959; (c) A. Tsotinis, M. Vlachou, D. P. Papahatjis, T. Calogeropoulou, S. P. Nikas, P. J. Garratt, V. Piccio, S. Vonhoff, K. Davidson, M.-T. Teh, D. Sugden, *J. Med. Chem.* **2006**, *49*, 3509–3519.
[133] L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990–12993. After reaction, the crude products were at first purified by flash chromatography and then by "bulb-to-bulb" distillation in order to remove the palladium residue.
[134] (a) P. Kazmierczak, L. Skulski, *Synthesis* **1995**, 1027–1032; (b) L. Kraszkiewicz, L. Skulski, *Synthesis* **2008**, 2373–2389.
[135] (a) K. S. Daub, B. Habermann, T. Hahn, L. Teich, K. Eger, *Eur. J. Org. Chem.* **2004**, 894–898; (b) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford, P. J. H. Scott, *Org. Lett.* **2014**, *16*, 3224–3227.
[136] M. Zhu, N. Jalalian, B. Olofsson, *Synlett* **2008**, *4*, 592–596.
[137] (a) G. W. Kabalka, E. E. Gooch, H. C. Hsu, *Synth. Commun.* **1981**, *11*, 247–251; (b) M. Ochiai, M. Toyonari, T. Nagaoka, D.-W. Chen, M. Kida, *Tetrahedron Lett.* **1997**, *38*, 6709–6712.

(**26p**),[138] oligopeptides **99a–d**,[139] **99f–g**, **99i**, **101a–c**, **101e–f**.

The following compounds were obtained by the generous courtesy of the persons named below:

M.Sc. Jasper Ploog: Peptide **99e**, **99h**.

M.Sc. Michaela Bauer: Peptide **101e**.

5.3 General Procedures

General procedure A for palladium-catalyzed C–H alkynylations of oxazoles with *gem*-dichloroalkenes:

A mixture of oxazole **8** (0.50 mmol), *gem*-dichloroalkene **94** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol %), DPE-Phos (6.0 mol %) and Li*O*tBu (2.5 mmol) in 1,4-dioxane (2.0 mL) was stirred at 120 °C for 14 h. At ambient temperature, H_2O (5 mL) was added, and the aqueous layer was extracted with EtOAc (4 × 20 mL). The organic layers were combined, and the solvents were removed *in vacuo*. Purification of the residue by column chromatography on silica gel yielded the product **9.**

General procedure B for metal-free C–H arylations of indolylacetamides and metal-free synthesis of pyrroloindolones:

A mixture of indolylacetamide **95** or **97** (0.50 mmol), diphenyliodonium tosylate **26** (0.75 mmol) in DMF (2.00 mL) was stirred at 100 °C for 17 h. At ambient temperature, H_2O (5 mL) was added, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel to yield the desired product **96** or **98**.

General procedure C for metal-free C–H arylations of peptide-containing indolylacetamides with diaryliodonium salts:

A mixture of peptide **99** (0.250 mmol), diaryliodonium tosylate **26** (0.375 mmol) in DMF

[138] C. A. Ocasio, T. S. Scanlan, *Bioorg. Med. Chem.* **2008**, *16*, 762–770; (b) J. Morgan, J. T. Pinhey, *J. Chem. Soc., Perkin. Trans. 1* **1993**, 1673–1676.

[139] (a) Z.-L. Shen, K. K. K. Goh, C. H. A. Wong, W.-Y. Loo, Y.-S. Yang, J. Lu, T.-P. Loh, *Chem. Commun.* **2012**, *48*, 5856–5858; (b) M. N. Kumara, D. C. Gowda, K. S. Rangappa, *Int. J. Chem. Kinet.* **2002**, *34*, 438–444; (c) S. M. Voshell, S. J. Lee, M. R. Gagné, *J. Am. Chem. Soc.* **2006**, *128*, 12422–12423.

(2.00 mL) was stirred at 100 °C for 17 h. At ambient temperature, the crude reaction mixture was directly purified by column chromatography on silica gel to yield the desired product **100**.

General procedure D1 for palladium-catalyzed C–H arylations of tryptophan-containing peptides with symmetrical diaryliodonium salts in AcOH:

A mixture of tryptophan-containing peptide **101** (0.20 mmol), symmetrical diaryliodonium tosylate **26** (0.30 mmol) and $Pd(OAc)_2$ (5.0 mol %) in AcOH (3.00 mL) was stirred at 23 °C for 17 h. At ambient temperature, H_2O (5 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, and the solvents were removed *in vacuo*. The crude product was purified by column chromatography on silica gel to yield the desired product **102**.

General procedure D2 for palladium-catalyzed C–H arylations of tryptophan-containing peptides with unsymmetrical diaryliodonium salts in AcOH/DCE:

A mixture of tryptophan-containing peptide **101** (0.2 mmol), unsymmetrical diaryliodonium tosylate **26** (0.3 mmol) and $Pd(OAc)_2$ (5.0 mol %) in mixture solvent of AcOH (1.5 mL) and DCE (1.5 mL) was stirred at 23 °C for 24 h. At ambient temperature, H_2O (5 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, and the solvents were removed *in vacuo*. The crude product was purified by column chromatography on silica gel to yield the desired product **102**.

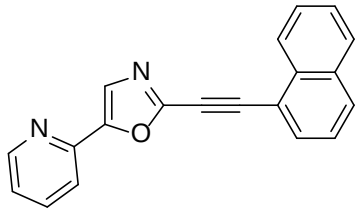
General procedure D3 for palladium-catalyzed C–H arylations of tryptophan-containing peptides with water as the reaction medium:

A mixture of tryptophan-containing peptide **101** (0.2 mmol), diaryliodonium tosylate **26** (0.3 mmol) and $Pd(OAc)_2$ (5.0 mol %) with water (3.0 mL) was stirred at 23 °C for 24 h. After the reaction was completed, MeOH (5.0 mL) was added, and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel to yield the desired product **102**.

5.4 Analytical Data

5.4.1 Analytical Data for Alkynylated Oxazoles

Synthesis of 2-(Naphthalen-1-ylethynyl)-5-(pyridin-2-yl)oxazole (9ba):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)naphthalene (**94a**) (167 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9ba** (130 mg, 88%) as a pale yellow solid (m. p. = 146–147 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.89 (d, *J* = 7.3 Hz, 1H), 7.82 (s, 1H), 7.78 (ddd, *J* = 7.9, 7.4, 1.6 Hz, 1H), 7.75 (ddd, *J* = 7.9, 1.1, 0.9 Hz, 1H), 7.65 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.57 (dd, *J* = 7.3, 6.8 Hz, 1H), 7.49 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.27 (ddd, *J* = 7.4, 4.7, 1.1 Hz, 1H).

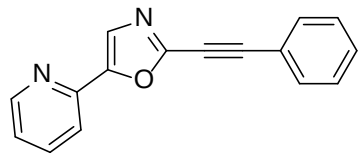
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5 (C_q), 150.0 (CH), 146.9 (C_q), 146.7 (C_q), 136.9 (CH), 133.2 (C_q), 133.0 (C_q), 131.9 (CH), 130.6 (CH), 128.4 (CH), 127.5 (CH), 126.8 (CH), 126.7 (CH), 125.9 (CH), 125.1 (CH), 123.3 (CH), 119.6 (CH), 118.1 (C_q), 90.8 (C_q), 81.8 (C_q).

IR (ATR): 3093, 2210, 1600, 1333, 1217, 947, 785, 763, 741, 485 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 296 (100) $[M]^+$, 268 (10), 163 (31), 119 (50), 91 (28).

HR-MS (EI) *m*/*z* calcd for $C_{20}H_{12}N_2O^+$ 296.0950, found 290.0945 $[M]^+$.

Synthesis of 2-(Phenylethynyl)-5-(pyridin-2-yl)oxazole (9bb):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and (2,2-dichlorovinyl)benzene (**94b**) (130 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9bb** (79 mg, 64%) as a pale yellow solid (m. p. = 86–87 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.77 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.76 (s, 1H), 7.70 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.73 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.44–7.34 (m, 3H), 7.25 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.4 (C_q), 150.0 (CH), 146.8 (C_q), 146.7 (C_q), 136.9 (CH),

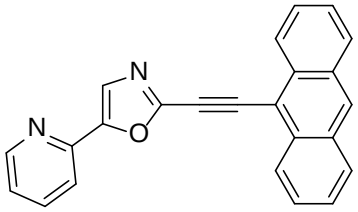
132.2 (CH), 130.0 (CH), 128.5 (CH), 126.6 (CH), 123.2 (CH), 120.5 (C_q), 119.5 (CH), 92.3 (C_q), 77.2 (C_q).

IR (ATR): 3098, 2222, 1758, 1601, 1524, 1161, 1080, 785, 688, 398 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 246 (100) $[M]^+$, 218 (13), 140 (10), 119 (62), 113 (30), 91 (36).

HR-MS (EI) *m*/*z* calcd for $C_{16}H_{10}N_2O^+$ 246.0793, found 246.0792 $[M]^+$.

Synthesis of 2-(Anthracen-9-ylethynyl)-5-(pyridin-2-yl)oxazole (9bc):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 9-(2,2-dichlorovinyl)anthracene (**94c**) (204 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9bc** (106 mg, 61%) as a pale yellow solid (m. p. = 183–184 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.61 (d, *J* = 8.6 Hz, 2H), 8.48 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.85 (s, 1H), 7.78–7.75 (m, 2H), 7.63 (dd, *J* = 8.6, 6.5 Hz, 2H), 7.51 (dd, *J* = 7.9, 6.5 Hz, 2H), 7.25 (dd, *J* = 7.4, 4.8 Hz, 1H).

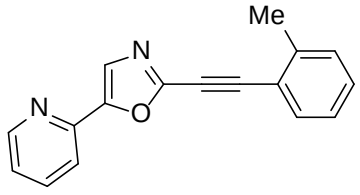
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5 (C_q), 150.0 (CH), 147.1 (C_q), 146.7 (C_q), 136.9 (CH), 133.4 (C_q), 130.9 (C_q), 129.9 (CH), 128.8 (CH), 127.5 (CH), 127.0 (CH), 126.3 (CH), 125.9 (CH), 123.3 (CH), 119.6 (CH), 113.9 (C_q), 89.9 (C_q), 88.0 (C_q).

IR (ATR): 3090, 2213, 1597, 1520, 1114, 781, 735, 701, 619, 406 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 346 (100) $[M]^+$, 213 (23), 119 (27), 91 (21).

HR-MS (EI) *m*/*z* calcd for $C_{24}H_{14}N_2O^+$ 346.1106, found 346.1105 $[M]^+$.

Synthesis of 2-[(2-Methylphenyl)ethynyl]-5-(pyridin-2-yl)oxazole (9bd):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-2-methylbenzene (**94d**) (140 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9bd** (91 mg, 70%) as a pale yellow solid (m. p. = 114–116 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.76 (ddd, *J* = 7.9, 7.4,

1.6 Hz, 1H), 7.75 (s, 1H), 7.69 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 7.7, 5.4 Hz, 1H), 7.18 (dd, *J* = 7.9, 5.4 Hz, 1H), 7.25 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 2.52 (s, 3H).

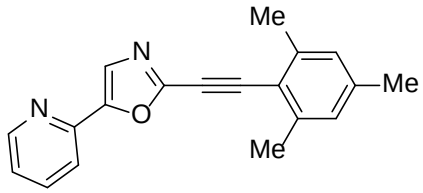
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.3 (C_q), 150.0 (CH), 146.9 (C_q), 146.7 (C_q), 141.4 (C_q), 136.9 (CH), 132.7 (CH), 130.0 (CH), 129.7 (CH), 126.7 (CH), 125.7 (CH), 123.2 (CH), 120.3 (C_q), 119.5 (CH), 91.4 (C_q), 80.8 (C_q), 20.7 (CH_3).

IR (ATR): 3097, 2213, 1719, 1603, 1576, 1469, 1337, 1198, 888, 791, 748, 455 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 260 (100) $[M]^+$, 154 (14), 127 (25), 119 (56), 91 (43).

HR-MS (EI) *m*/*z* calcd for $C_{17}H_{12}N_2O^+$ 260.0950, found 260.0946 $[M]^+$.

Synthesis of 2-[(2,4,6-Trimethylphenyl)ethynyl]-5-(pyridin-2-yl)oxazole (9be):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 2-(2,2-dichlorovinyl)-1,3,5-trimethylbenzene (**94e**) (161 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9be** (96 mg, 67%) as a pale yellow solid (m. p. = 128–129 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.78 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.77 (s, 1H), 7.71 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.25 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 6.91 (s, 2H), 2.49 (s, 6H), 2.29 (s, 3H).

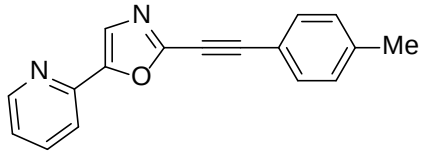
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2 (C_q), 150.0 (CH), 147.3 (C_q), 146.8 (C_q), 141.6 (C_q), 139.9 (C_q), 136.9 (CH), 127.9 (CH), 126.7 (CH), 123.1 (CH), 119.5 (CH), 117.4 (C_q), 90.7 (C_q), 84.4 (C_q), 21.4 (CH_3), 20.9 (CH_3).

IR (ATR): 3100, 2914, 2207, 1604, 1519, 1280, 1153, 1075, 846, 778, 709, 401 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 288 (100) $[M]^+$, 273 (10), 182 (11), 119 (25), 91 (20).

HR-MS (EI) *m*/*z* calcd for $C_{19}H_{16}N_2O^+$ 288.1263, found 288.1264 $[M]^+$.

Synthesis of 2-[(4-Methylphenyl)ethynyl]5-(pyridin-2-yl)oxazole (9bf):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-methylbenzene (**94f**) (140 mg,

0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 30/1→5/1) yielded **9bf** (55 mg, 42%) as a pale yellow solid (m. p. = 135–137 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.78 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.74 (s, 1H), 7.70 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.24 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 2.38 (s, 3H).

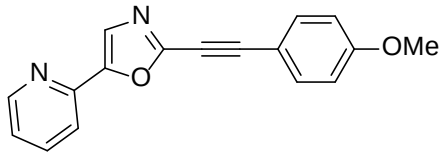
^{13}C NMR(75 MHz, $CDCl_3$): δ = 151.2 (C_q), 150.0 (CH), 146.9 (C_q), 146.7 (C_q), 140.5 (C_q), 136.9 (CH), 132.1 (CH), 129.3 (CH), 126.6 (CH), 123.2 (CH), 119.5 (CH), 117.4 (C_q), 92.7 (C_q), 76.8 (C_q), 21.6 (CH_3).

IR (ATR): 3086, 2913, 2215, 1601, 1528, 1279, 1160, 779, 742 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 260 (100) $[M]^+$, 232 (10), 127 (23), 119 (43), 91 (20).

HR-MS (EI) *m*/*z* calcd for $C_{17}H_{12}N_2O^+$ 260.0950, found 260.0950 $[M]^+$.

Synthesis of 2-[(4-Methoxyphenyl)ethynyl]-5-(pyridin-2-yl)oxazole (9bg):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (48 mg, 0.33 mmol) and 1-(2,2-dichlorovinyl)-4-methoxybenzene (**94g**) (101 mg, 0.50 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 30/1) yielded **9bg** (35 mg, 38%) as a pale yellow solid (m. p. = 103–105 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.77 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.74 (s, 1H), 7.70 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.24 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H).

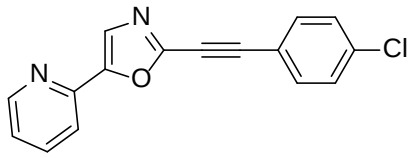
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0 (C_q), 151.1 (C_q), 150.0 (CH), 147.1 (C_q), 146.8 (C_q), 136.9 (CH), 133.9 (CH), 126.6 (CH), 123.2 (CH), 119.5 (CH), 114.3 (CH), 112.4 (C_q), 92.8 (C_q), 76.4 (C_q), 55.4 (CH_3).

IR (ATR): 3113, 2938, 2214, 1608, 1533, 1296, 1112, 781, 740 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 276 (100) $[M]^+$, 261 (9), 233 (10), 143 (26), 119 (54), 91 (29).

HR-MS (EI) *m*/*z* calcd for $C_{17}H_{12}N_2O_2^+$ 276.0899, found 276.0899 $[M]^+$.

Synthesis of 2-[(4-Chlorophenyl)ethynyl]-5-(pyridin-2-yl)oxazole (9bh):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 1-chloro-4-(2,2-dichlorovinyl)benzene (**94h**) (156 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9bh** (70 mg, 50%) as a pale yellow solid (m. p. = 137–138 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.77 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.75 (s, 1H), 7.70 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.25 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H).

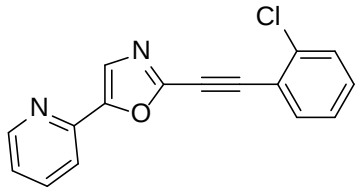
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5 (C_q), 150.0 (CH), 146.6 (C_q), 146.5 (C_q), 136.9 (CH), 136.2 (CH), 133.4 (CH), 129.0 (CH), 126.7 (CH), 123.3 (CH), 119.6 (C_q), 119.0 (CH), 91.1 (C_q), 78.1 (C_q).

IR (ATR): 3090, 2217, 1673, 1522, 1158, 823, 777, 707, 521 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 282/280 (32/100) $[M]^+$, 252 (12), 147 (25), 119 (75), 91 (41).

HR-MS (EI) *m*/*z* calcd for $C_{16}H_9ClN_2O^+$ 280.0403, found 280.0412 $[M]^+$.

Synthesis of 2-[(2-Chlorophenyl)ethynyl]-5-(pyridin-2-yl)oxazole (9bi):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 1-chloro-2-(2,2-dichlorovinyl)benzene (**94i**) (156 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9bi** (80 mg, 57%) as a pale yellow solid (m. p. = 128–129 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.78 (s, 1H), 7.77 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.74 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.28 (dd, *J* = 7.7, 7.6 Hz, 1H), 7.24 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H).

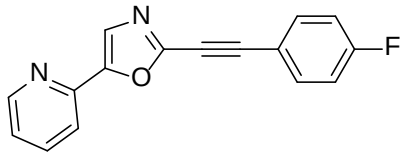
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6 (C_q), 150.0 (CH), 146.6 (C_q), 146.4 (C_q), 136.9 (CH), 136.6 (C_q), 134.0 (CH), 130.9 (CH), 129.5 (CH), 126.8 (CH), 126.6 (CH), 123.3 (CH), 120.8 (C_q), 119.6 (CH), 88.7 (C_q), 81.7 (C_q).

IR (ATR): 3095, 2222, 1603, 1521, 1284, 1030, 830, 790, 747, 403 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 282/280 (33/100) $[M]^+$, 252 (18), 147 (35), 119 (83), 91 (54).

HR-MS (EI) *m*/*z* calcd for $C_{16}H_9ClN_2O^+$ 280.0403, found 280.0413 $[M]^+$.

Synthesis of 2-[(4-Fluorophenyl)ethynyl]-5-(pyridin-2-yl)oxazole (9bj):



The general procedure A was followed using 5-(pyridin-2-yl)oxazole (**8b**) (73 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-fluorobenzene (**94j**) (143 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9bj** (61 mg, 46%) as a pale white solid (m. p. = 106–108 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 1H), 7.74 (s, 1H), 7.68 (ddd, *J* = 7.7, 1.1, 0.9 Hz, 1H), 7.60 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.24 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 7.08 (dd, *J* = 8.9, 8.5 Hz, 2H).

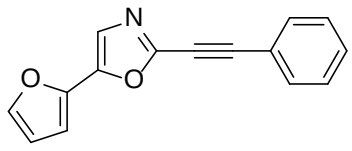
^{13}C NMR(75 MHz, $CDCl_3$): δ = 165.1 (C_q), 161.8 (C_q), 151.4 (C_q), 150.0 (CH), 146.5 (C_q), 136.9 (CH), 134.3 (d, J_{C-F} = 8.6 Hz, CH), 126.6 (CH), 123.3 (CH), 119.5 (CH), 116.6 (d, J_{C-F} = 3.4 Hz, C_q), 116.0 (d, J_{C-F} = 22.3 Hz, CH), 91.2 (C_q), 77.1 (C_q).

IR (ATR): 3096, 2219, 1601, 1530, 1336, 834, 779, 707 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 264 (100) $[M]^+$, 236 (10), 208 (8), 158 (11), 131 (32), 119 (62), 91 (35).

HR-MS (EI) *m*/*z* calcd for $C_{16}H_9FN_2O^+$ 264.0699, found 264.0699 $[M]^+$.

Synthesis of 5-(Furan-2-yl)-2-(phenylethynyl)oxazole (9cb):



The general procedure A was followed using 5-(furan-2-yl)oxazole (**8c**) (68 mg, 0.50 mmol) and (2,2-dichlorovinyl)benzene (**94b**) (130 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9cb** (54 mg, 46%) as a pale yellow solid (m. p. = 59–61 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.49 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.44–7.38 (m, 3H), 7.31 (s, 1H), 6.72 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.5 (C_q), 144.4 (C_q), 143.2 (CH), 143.1 (C_q), 132.2 (CH),

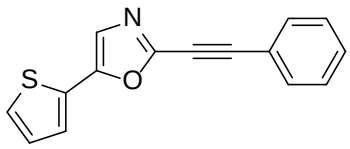
129.9 (CH), 128.5 (CH), 123.0 (CH), 120.6 (C_q), 111.7 (CH), 108.3 (CH), 92.2 (C_q), 77.2 (C_q).

IR (ATR): 3128, 2218, 1639, 1620, 1066, 1011, 741, 686 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 235 (100) $[M]^+$, 180 (44), 152 (58), 126 (39), 113 (19), 9 (11).

HR-MS (EI) *m*/*z* calcd for $C_{15}H_9NO_2^+$ 235.0633, found 235.0631 $[M]^+$.

Synthesis of 2-(Phenylethynyl)-5-(thiophen-2yl)oxazole (9db):



The general procedure A was followed using 5-(thiophen-2-yl)oxazole (**8d**) (76 mg, 0.50 mmol) and (2,2-dichlorovinyl)benzene (**94b**) (130 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 30/1) yielded **9db** (65 mg, 52%) as a pale yellow solid (m. p. = 91–92 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 7.5, 1.4 Hz, 2H), 7.45–7.35 (m, 5H), 7.27 (s, 1H), 7.10 (dd, *J* = 4.8, 3.4 Hz, 1H).

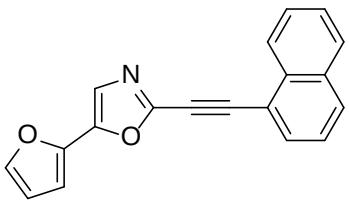
^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6 (C_q), 145.5 (C_q), 132.2 (CH), 129.9 (CH), 129.2 (C_q), 128.5 (CH), 127.9 (CH), 126.3 (CH), 125.1 (CH), 122.9 (CH), 120.6 (C_q), 92.1 (C_q), 77.1 (C_q).

IR (ATR): 3107, 2216, 1530, 1164, 1017, 848, 759, 691, 524 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 251 (90) $[M]^+$, 196 (100), 152 (35), 110 (25).

HR-MS (EI) *m*/*z* calcd for $C_{15}H_9NOS^+$ 251.0405, found 281.0400 $[M]^+$.

Synthesis of 5-(Furan-2-yl)-2-(103aphthalene-1-ylethynyl)oxazole (9ca):



The general procedure A was followed using 5-(furan-2-yl)oxazole (**8c**) (68 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)naphthalene (**94a**) (167 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9ca** (110 mg, 77%) as a pale yellow solid (m. p. = 78–79 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 7.3 Hz, 1H), 7.64 (dd, *J* = 8.0, 6.7 Hz, 1H), 7.57 (dd, *J* = 8.4, 6.7 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.49 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.37 (s, 1H), 6.77 (d, *J* =

3.4 Hz, 1H), 6.54 (dd, *J* = 3.4, 1.9 Hz, 1H).

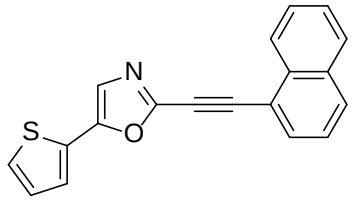
^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6 (C_q), 144.4 (C_q), 143.3 (CH), 143.1 (C_q), 133.2 (C_q), 133.0 (C_q), 131.8 (CH), 130.5 (CH), 128.4 (CH), 127.4 (CH), 126.8 (CH), 125.9 (CH), 125.1 (CH), 123.2 (CH), 118.1 (C_q), 111.8 (CH), 108.4 (CH), 90.7 (C_q), 81.6 (C_q).

IR (ATR): 3058, 2211, 1636, 1584, 1199, 1011, 885, 798, 772, 705 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 285 (100) $[M]^+$, 230 (45), 202 (38), 176 (42), 163 (18).

HR-MS (EI) *m*/*z* calcd for $C_{19}H_{11}NO_2^+$ 285.0790, found 285.0798 $[M]^+$.

Synthesis of 2-(Naphthalen-1-ylethynyl)-5-(thiophen-2-yl)oxazole (9da):



The general procedure A was followed using 5-(thiophen-2-yl)oxazole (**8d**) (76 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)naphthalene (**94a**) (167 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded **9da** (100 mg, 66%) as a pale yellow solid (m. p. = 98–99 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.64 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.56 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.48 (dd, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 3.8 Hz, 1H), 7.38 (d, *J* = 5.1 Hz, 1H), 7.32 (s, 1H), 7.11 (dd, *J* = 5.1, 3.8 Hz, 1H).

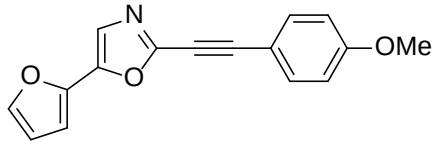
^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7 (C_q), 145.6 (C_q), 133.2 (C_q), 133.0 (C_q), 131.8 (CH), 130.5 (CH), 129.2 (C_q), 128.4 (CH), 128.0 (CH), 127.4 (CH), 126.8 (CH), 126.4 (CH), 125.9 (CH), 125.1 (CH), 123.0 (CH), 118.2 (C_q), 90.6 (Cq), 81.7 (C_q).

IR (ATR): 3102, 2216, 1586, 1117, 911, 845, 796, 767, 705, 436 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 301 (92) $[M]^+$, 245 (100), 163 (35), 111 (32).

HR-MS (EI) *m*/*z* calcd for $C_{19}H_{11}NOS^+$ 301.0561, found 301.0556 $[M]^+$.

Synthesis of 5-(Furan-2-yl)-2-[(4-methoxyphenyl)ethynyl]oxazole (9cg):



The general procedure A was followed using 5-(furan-2-yl)oxazole (**8c**) (68 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-methoxybenzene (**94g**) (152 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 30/1) yielded **9cg** (75 mg, 57%) as a pale yellow solid (m. p. = 105–106 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.6, 2H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.29 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 3.5 Hz, 1H), 6.51 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.83 (s, 3H).

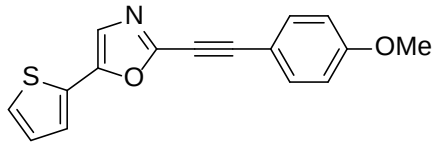
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9 (C_q), 145.8 (C_q), 144.1 (C_q), 143.2 (C_q), 143.1 (CH), 133.8 (CH), 123.0 (CH), 114.2 (CH), 112.5 (C_q), 111.7 (CH), 108.1 (CH), 92.6 (C_q), 76.1 (C_q), 55.4 (CH_3).

IR (ATR): 3040, 2216, 1603, 1545, 1248, 1160, 1010, 963, 837, 744, 557 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 265 (100) $[M]^+$, 210 (80), 182 (44), 156 (61), 143 (33), 95 (38).

HR-MS (EI) *m*/*z* calcd for $C_{16}H_{11}NO_3^+$ 265.0739, found 265.0735 $[M]^+$.

Synthesis of 2-[(4-Methoxyphenyl)ethynyl]-5-(thiophen-2-yl)oxazole (9dg):



The general procedure A was followed using 5-(thiophen-2-yl)oxazole (**8d**) (76 mg, 0.50 mmol) and 1-(2,2-dichlorovinyl)-4-methoxybenzene (**94g**) (152 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 30/1) yielded **9dg** (80 mg, 57%) as a pale yellow solid (m. p. = 96–97 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 5.0 Hz, 1H), 7.33 (d, *J* = 3.5 Hz, 1H), 7.26 (s, 1H), 7.10 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.82 (s. 3H).

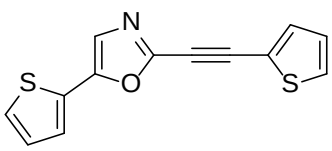
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9 (C_q), 147.3 (C_q), 145.8 (C_q), 133.8 (CH), 129.3 (C_q), 127.9 (CH), 126.2 (CH), 124.9 (CH), 122.8 (CH), 114.2 (CH), 112.6 (C_q), 92.5 (C_q), 76.1 (C_q), 55.4 (CH_3).

IR (ATR): 3078, 2214, 1602, 1535, 1248, 1175, 1016, 823, 704, 568 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 281 (90) $[M]^+$, 226 (100), 211 (26), 183 (15), 111 (22).

HR-MS (EI) *m*/*z* calcd for $C_{16}H_{11}NO_2S^+$ 281.0510, found 281.0511 $[M]^+$.

Synthesis of 5-(Thiophen-2-yl)-2-(thiophen-2-ylethynyl)oxazole (9dm):



The general procedure A was followed using 5-(thiophen-2-yl)oxazole (**8d**) (76 mg, 0.50 mmol) and 2-(2,2-dichlorovinyl)thiophene (**94m**) (134 mg, 0.75 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 30/1) yielded **9dm** (45 mg, 35%)

as a pale yellow solid (m. p. = 110–111 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 5.1 Hz, 1H), 7.44 (d, *J* = 3.6 Hz, 1H), 7.36 (d, *J* = 5.3 Hz, 1H), 7.35 (d, *J* = 3.4 Hz, 1H), 7.27 (s, 1H), 7.04 (d, *J* = 5.1, 3.6 Hz, 1H), 7.08 (dd, *J* = 5.3, 3.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7 (C_q), 145.4 (C_q), 134.6 (CH), 129.6 (CH), 129.2 (C_q), 127.9 (CH), 127.4 (CH), 126.4 (CH), 125.2 (CH), 123.1 (CH), 120.6 (C_q), 85.8 (C_q), 80.9 (C_q).

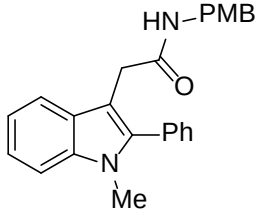
IR (ATR): 3075, 2203, 1589, 1410, 1211, 1019, 824, 715, 486 cm^{-1}.

MS (EI) *m*/*z* (relative intensity) 257 (88) $[M]^+$, 202 (100), 158 (30), 119 (26), 110 (24), 69 (41).

HR-MS (EI) *m*/*z* calcd for $C_{13}H_7NOS_2^+$ 256.9969, found 256.9972 $[M]^+$.

5.4.2 Analytical Data for Arylated Indolylacetamides

Synthesis of *N*-(4-Methoxybenzyl)-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acetamide (96ah):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ah** (184 mg, 96%) as a pale white solid (m. p. = 157–158 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (ddd, *J* = 7.8, 1.1, 0.9 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37 (ddd, *J* = 8.2, 1.3, 0.9 Hz, 1H), 7.30 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.27 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.19 (ddd, *J* = 7.8, 6.9, 1.3 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.98 (t, *J* = 5.9 Hz, 1H), 4.31 (d, *J* = 5.9 Hz, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 3.62 (s, 3H).

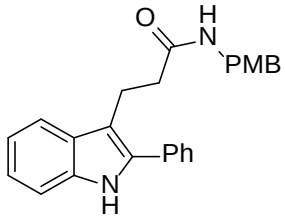
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C_q), 158.8 (C_q), 139.9 (C_q), 137.3 (C_q), 130.7 (C_q), 130.4 (C_q), 130.3 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.3 (C_q), 122.4 (CH), 120.1 (CH), 118.8 (CH), 113.8 (CH), 109.6 (CH), 105.7 (C_q), 55.3 (CH_3), 42.8 (CH_2), 32.9 (CH_2), 31.0 (CH_3).

IR (ATR): 3244, 1631, 1512, 1254, 1175, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity) 384 (23) $[M]^+$, 220 (100), 204 (22), 121 (14).

HR-MS (EI): *m/z* calcd for $C_{25}H_{24}N_2O_2^+$ 384.1838, found 384.1837 $[M]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-3-(2-phenyl-1*H*-indol-3-yl)propanamide (96bh):



The general procedure B was followed using 3-(1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)propanamide (**95b**) (154 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96bh** (42 mg, 22%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (s, 1H), 7.64 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.44 (dd,*J* = 8.5, 7.5 Hz, 2H), 7.38 (dd, *J* =8.1, 1.3 Hz, 1H), 7.36 (d, *J* =7.5 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.8, 7.0, 1.3 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.54 (t, *J* = 5.8 Hz, 1H), 4.23 (d, *J* = 5.8 Hz, 2H), 3.77 (s, 3H), 3.28 (t, *J* = 8.6 Hz, 2H), 2.55 (t, *J* = 8.6 Hz, 2H).

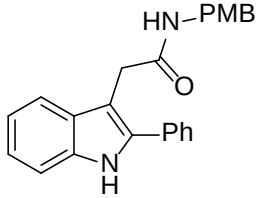
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (C_q), 158.8(C_q), 135.8 (C_q), 134.6 (C_q), 132.8 (C_q), 130.1 (C_q), 129.0 (CH), 128.9 (CH), 128.7 (C_q), 127.9 (CH), 127.7 (CH), 122.3 (CH), 119.7 (CH), 119.0 (CH), 113.9 (CH), 111.5 (C_q), 110.9 (CH), 55.2 (CH_3), 43.0 (CH_2), 37.4 (CH_2), 20.7 (CH_2).

IR (ATR): 3279, 1644, 1510, 1242, 1174, 1029, 743, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity) 384 (51) $[M]^+$, 234 (19), 222 (30), 206 (100), 178 (23), 136 (33), 121 (64).

HR-MS (EI): *m/z* calcd for $C_{25}H_{24}N_2O_2^+$ 384.1838, found 384.1825 $[M]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-2-(2-phenyl-1*H*-indol-3-yl)acetamide (96ch):



The general procedure B was followed using 2-(1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**95c**) (147 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ch** (166 mg, 90%) as a pale white solid (m. p. =

165–166 °C).

^{1}H NMR (300 MHz, d_6-DMSO): δ = 11.2 (s, 1H), 8.42 (t, J = 5.9 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.59 (dd, J = 7.8, 1.1 Hz, 1H), 7.48 (dd, J = 8.5, 7.5 Hz, 2H), 7.40 (dd, J = 8.1, 1.3 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.11 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.00 (ddd, J = 7.8, 7.0, 1.3 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 4.24 (d, J = 5.8 Hz, 2H), 3.73 (s, 3H), 3.67 (s, 2H).

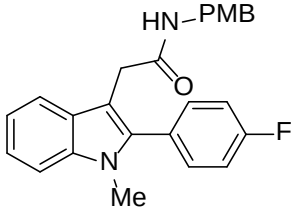
^{13}C NMR (75 MHz, d_6-DMSO): δ = 170.6 (C_q), 158.1 (C_q), 135.9 (C_q), 135.8 (C_q), 132.5 (C_q), 131.5 (C_q), 128.9 (C_q), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 121.4 (CH), 118.8 (CH), 118.6 (CH), 113.6 (CH), 111.0 (CH), 106.0 (C_q), 55.0 (CH_3), 41.8 (CH_2), 31.8 (CH_2).

IR (ATR): 3385, 1638, 1508, 1240, 1175, 1028, 815, 746, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity) 370 (31) $[M]^+$, 206 (100), 193 (60), 121 (40).

HR-MS (EI): *m/z* calcd for $C_{24}H_{22}N_2O_2^+$ 370.1681, found 370.1682 $[M]^+$.

Synthesis of 2-[2-(4-Fluorophenyl)-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)-acetamide (96ai):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and bis(4-fluorophenyl)iodonium tosylate (**26i**) (366 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ai** (191 mg, 95%) as a pale white solid (m. p. = 150–151 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, J = 7.8, 1.1 Hz, 1H), 7.37 (dd, J = 8.2, 1.3 Hz, 1H), 7.34–7.23 (m, 3H), 7.23–7.10 (m, 3H), 7.0 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.98 (t, J = 5.9 Hz, 1H), 4.31 (d, J = 5.9 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 2H), 3.60 (s, 3H).

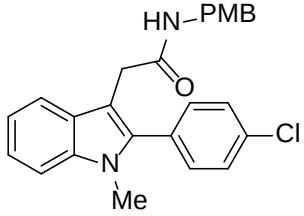
^{13}C NMR (75 MHz, $CDCl_3$): δ= 171.2 (C_q), 162.9 (C_q, J_{C-F} = 249.3 Hz), 158.8 (C_q), 138.7 (C_q), 137.2 (C_q), 132.1 (CH, J_{C-F} = 8.3 Hz), 130.4 (C_q), 128.8 (CH), 127.2 (C_q), 126.7 (C_q, J_{C-F} = 3.2 Hz), 122.5 (CH), 120.2 (CH), 118.8 (CH), 115.8 (CH, J_{C-F} = 22.2 Hz), 113.8 (CH), 109.6 (CH), 105.9 (C_q), 55.2 (CH_3), 42.8 (CH_2), 32.8 (CH_2), 30.9 (CH_3).

IR (ATR): 3281, 1639, 1504, 1255, 1220, 1027, 846, 739 cm^{-1}.

MS (EI) *m/z* (relative intensity) 402 (26) $[M]^+$, 238 (100), 222 (21), 121 (14).

HR-MS (EI): *m/z* calcd for $C_{25}H_{23}FN_2O_2^+$ 402.1744, found 402.1744 $[M]^+$.

Synthesis of 2-[2-(4-Chlorophenyl)-1-methyl-1*H*-indol-3-yl]-*N*-(4-methoxybenzyl)-acetamide (96aj):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and bis(4-chlorophenyl)iodonium tosylate (**26j**) (391 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96aj** (187 mg, 89%) as a pale white solid (m. p. = 167–168 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.35 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.3, 6.8, 1.1 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.19 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.95 (t, *J* = 5.9 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 2H), 3.79 (s, 3H), 3.68 (s, 2H), 3.61 (s, 3H).

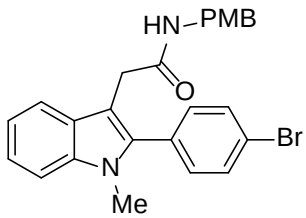
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (C_q), 158.8 (C_q), 138.5 (C_q), 137.3 (C_q), 134.8 (C_q), 131.5 (CH), 130.3 (C_q), 129.1 (C_q), 129.0 (CH), 128.8 (CH), 127.2 (C_q), 122.7 (CH), 120.3 (CH), 118.8 (CH), 113.8 (CH), 109.7 (CH), 106.1 (C_q), 55.3 (CH_3), 42.8 (CH_2), 32.8 (CH_2), 31.0 (CH_3).

IR (ATR): 3280, 1638, 1547, 1513, 1255, 1028, 741 cm^{-1}.

MS (EI) *m/z* (relative intensity) 420/418 (8/26) $[M]^+$, 256/254 (32/100), 219 (67), 121 (34).

HR-MS (EI): *m/z* calcd for $C_{25}H_{23}ClN_2O_2^+$ 418.1448, found 418.1437 $[M]^+$.

Synthesis of 2-[2-(4-Bromophenyl)-1-methyl-1*H*-indol-3-yl]-*N*-(4-methoxybenzyl)-acetamide (96ak):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and bis(4-bromophenyl)iodonium tosylate (**26k**) (458 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ak** (215 mg, 93%) as a pale white solid (m. p. = 187–189 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.4 Hz, 2H), 7.59 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.36 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.31 (ddd, *J* = 8.3, 6.7, 1.1 Hz, 1H), 7.19 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.95 (t, *J* = 5.9 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 2H), 3.79 (s, 3H), 3.68 (s, 2H), 3.61 (s, 3H).

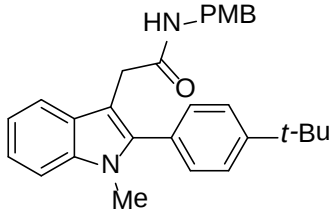
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (C_q), 158.8 (C_q), 138.5 (C_q), 137.3 (C_q), 132.0 (CH), 131.8 (CH), 130.3 (C_q), 129.6 (C_q), 128.8 (CH), 127.2 (C_q), 123.0 (C_q), 122.7 (CH), 120.3 (CH), 118.8 (CH), 113.8 (CH), 109.7 (CH), 106.1 (C_q), 55.3 (CH_3), 42.8 (CH_2), 32.8 (CH_2), 31.0 (CH_3).

IR (ATR): 3243, 1629, 1556, 1513, 1242, 1175, 834, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity) 464/462 (29/28) $[M]^+$, 300/298 (99/100), 219 (96), 204 (27), 121 (49).

HR-MS (EI): *m/z* calcd for $C_{25}H_{23}BrN_2O_2^+$ 462.0943, found 462.0952 $[M]^+$.

Synthesis of 2-{2-[4-(*tert*-Butyl)phenyl]-1-methyl-1*H*-indol-3-yl}-*N*-(4-methoxybenzyl)acetamide (96al):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and bis(4-*tert*-butylphenyl)-iodonium tosylate (**26l**) (423 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96al** (183 mg, 83%) as a pale white solid (m. p. = 139–140 °C).

^{1}H NMR(300 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.35 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.29 (ddd, *J* = 8.3, 6.7, 1.1 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.18 (ddd, *J* = 8.0, 6.7, 1.3 Hz, 1H), 7.05 (d, *J* = 9.1 Hz, 2H), 6.78 (d, *J* = 9.1 Hz, 2H), 6.02 (t, *J* = 6.0 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.71 (s, 2H), 3.63 (s, 3H), 1.39 (s, 9H).

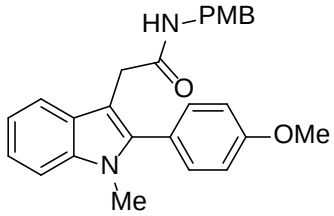
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 (C_q), 158.8 (C_q), 151.6 (C_q), 140.1 (C_q), 137.2 (C_q), 130.5 (C_q), 129.9 (CH), 128.8 (CH), 127.6 (C_q), 127.4 (C_q), 125.6 (CH), 122.2 (CH), 120.0 (CH), 118.7 (CH), 113.8 (CH), 109.6 (CH), 105.5 (C_q), 55.2 (CH_3), 42.8 (CH_2), 34.7 (C_q), 33.0 (CH_2), 31.3 (CH_3), 31.0 (CH_3).

IR (ATR): 3262, 2959, 1641, 1511, 1245, 1038, 733 cm^{-1}.

MS (EI) *m/z* (relative intensity) 440 (34) $[M]^+$, 276 (100), 220 (66), 121 (26).

HR-MS (EI): *m/z* calcd for $C_{29}H_{32}N_2O_2^+$ 440.2464, found 440.2471 $[M]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-2-[2-(4-methoxyphenyl)-1-methyl-1*H*-indol-3-yl]-acetamide (96ag):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and bis(4-methoxyphenyl)-iodonium tosylate (**26g**) (384 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ag** (175 mg, 84%) as a pale white solid (m. p. = 153–154 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.35 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.28 (ddd, *J* = 8.3, 6.7, 1.1 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.18 (ddd, *J* = 8.0, 6.7, 1.3 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 6.01 (t, *J* = 6.0 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 3.70 (s, 2H), 3.61 (s, 3H).

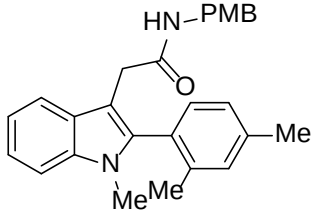
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5 (C_q), 159.8 (C_q), 158.7 (C_q), 139.8 (C_q), 137.1 (C_q), 131.5 (CH), 130.4 (C_q), 128.8 (CH), 127.3 (C_q), 122.8 (C_q), 122.2 (CH), 120.0 (CH), 118.6 (CH), 114.2 (CH), 113.8 (CH), 109.5 (CH), 105.3 (C_q), 55.3 (CH_3), 55.2 (CH_3), 42.8 (CH_2), 32.9 (CH_2), 30.8 (CH_3).

IR (ATR): 3258, 2935, 2836, 1626, 1611, 1507, 1243, 1029, 841, 746 cm^{-1}.

MS (EI) *m/z* (relative intensity) 414 (23) $[M]^+$, 250 (100), 219 (17), 121 (16).

HR-MS (EI): *m/z* calcd for $C_{26}H_{26}N_2O_3^+$ 414.1943, found 414.1942 $[M]^+$.

Synthesis of 2-[2-(2,4-Dimethylphenyl)-1-methyl-1*H*-indol-3-yl]-*N*-(4-methoxybenzyl)acetamide (96am):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and bis(2,4-dimethylphenyl)iodonium tosylate (**26m**) (381 mg, 0.75 mmol). After 17 h, purification by

column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96am** (130 mg, 63%) as a pale white solid (m. p. = 160–161 °C).

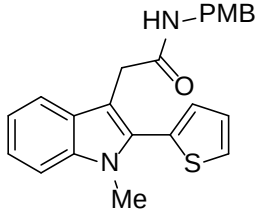
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.29 (dd, *J* = 8.0, 6.7 Hz, 1H), 7.19 (dd, *J* = 8.2, 6.7 Hz, 1H), 7.14 (s, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.02 (t, *J* = 6.0 Hz, 1H), 4.34 (dd, *J* = 14.7, 6.0 Hz, 1H), 4.25 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.79 (s, 3H), 3.66 (d, *J* = 17.4 Hz, 1H), 3.50 (d, *J* = 17.4 Hz, 1H), 3.47 (s, 3H), 2.41 (s, 3H), 1.98 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3 (C_q), 158.7 (C_q), 139.6 (C_q), 139.1 (C_q), 138.0 (C_q), 136.9 (C_q), 131.0 (CH), 130.9 (CH), 130.3 (C_q), 128.8 (CH), 127.3 (C_q), 127.2 (C_q), 126.6 (CH), 121.9 (CH), 119.8 (CH), 118.7 (CH), 113.7 (CH), 109.4 (CH), 105.4 (C_q), 55.2 (CH_3), 42.7 (CH_2), 32.7 (CH_2), 30.2 (CH_3), 21.2 (CH_3), 19.4 (CH_3).

IR (ATR): 3251, 2923, 1633, 1513, 1256, 1032, 831, 747 cm^{-1}.

MS (EI) *m/z* (relative intensity) 412 (24) $[M]^+$, 248 (100), 233 (26), 218 (25), 121 (15). **HR-MS** (EI): *m/z* calcd for $C_{27}H_{28}N_2O_2^+$ 412.2151, found 412.2152 $[M]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-2-[1-methyl-2-(thiophen-2-yl)-1*H*-indol-3-yl]-acetamide (96ao):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol) and di(thiophen-2-yl)iodonium tosylate (**26o**) (348 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ao** (127 mg, 65%) as a pale white solid (m. p. = 158–160 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.50 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.2, 6.7, 1.0 Hz, 1H), 7.19 (ddd, *J* = 7.9, 6.7, 1.3 Hz, 1H), 7.16 (dd, *J* = 5.2, 3.8 Hz, 1H), 7.06 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.96 (t, *J* = 5.9 Hz, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 3.79 (s, 2H), 3.77 (s, 3H), 3.70 (s, 3H).

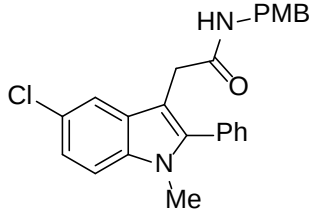
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (C_q), 158.7 (C_q), 137.4 (C_q), 132.2 (C_q), 130.8 (C_q), 130.3 (C_q), 129.5 (CH), 128.7 (CH), 127.8 (CH), 127.5 (CH), 127.0 (C_q), 122.9 (CH), 120.2

(CH), 118.9 (CH), 113.8 (CH), 109.7 (CH), 108.0 (C_q), 55.2 (CH_2), 42.8 (CH_2), 33.1 (CH_2), 30.9 (CH_3).

IR (ATR): 3240, 3071, 1628, 1513, 1463, 1255, 1229, 1032, 816, 747, 705 cm^{-1}.

MS (EI) *m/z* (relative intensity) 390 (29) $[M]^+$, 226 (100), 213 (15), 210 (11), 121 (19). **HR-MS** (EI): *m/z* calcd for $C_{23}H_{22}N_2O_2S^+$ 390.1402, found 390.1402 $[M]^+$.

Synthesis of 2-(5-Chloro-1-methyl-2-phenyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)-acetamide (96gh):



The general procedure B was followed using 2-(5-chloro-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)-acetamide (**95g**) (172 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96gh** (101 mg, 48%) as a pale white solid (m. p. = 156–157 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 1.9 Hz, 1H), 7.50–7.46 (m, 3H), 7.33–7.28 (m, 2H), 7.25–7.23 (m, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.92 (t, *J* = 5.8 Hz, 1H), 4.32 (d, *J* = 5.8 Hz, 2H), 3.78 (s, 3H), 3.63 (s, 2H), 3.59 (s, 3H).

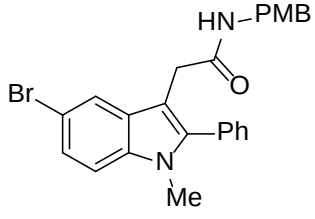
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (C_q), 158.8 (C_q), 141.1 (C_q), 135.6 (C_q), 130.3 (C_q), 130.3 (C_q), 130.2 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.3 (C_q), 125.8 (C_q), 122.6 (CH), 118.3 (CH), 113.9 (CH), 110.7 (CH), 105.5 (C_q), 55.2 (CH_3), 42.9 (CH_2), 32.8 (CH_2), 31.2 (CH_3).

IR (ATR): 3283, 1645, 1512, 1469, 1253, 1226, 1110, 853, 784, 707 cm^{-1}.

MS (EI) *m/z* (relative intensity) 420/418 (7/23) $[M]^+$, 256/254 (32/100), 220/218 (10/32), 121 (21).

HR-MS (EI): *m/z* calcd for $C_{25}H_{23}ClN_2O_2^+$ 418.1448, found 418.1438 $[M]^+$.

Synthesis of 2-(5-Bromo-1-methyl-2-phenyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)-acetamide (96hh):



The general procedure B was followed using 2-(5-bromo-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)-acetamide (**95h**) (194 mg, 0.50 mmol) and diphenyliodonium

tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96hh** (130 mg, 56%) as a pale white solid (m. p. = 157–158 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 1.9 Hz, 1H), 7.48–7.43(m, 3H), 7.35 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.28 (dd, *J* = 7.6, 3.5 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 5.91 (t, *J* = 5.8 Hz, 1H), 4.33 (d, *J* = 5.8 Hz, 2H), 3.78 (s, 3H), 3.63 (s, 2H), 3.59 (s, 3H).

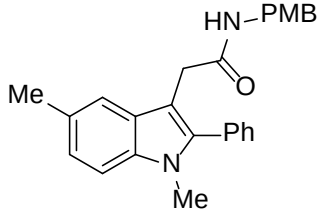
^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (C_q), 158.8 (C_q), 141.0 (C_q), 135.9 (C_q), 130.2 (CH), 130.2 (C_q), 128.9 (C_q), 128.9 (C_q), 128.9 (C_q), 128.8 (CH), 128.8 (CH), 125.2 (CH), 121.4 (CH), 113.9 (CH), 113.3 (CH), 111.2 (CH), 105.3 (C_q), 55.26 (CH_3), 42.87 (CH_2), 32.73 (CH_2), 31.13 (CH_3).

IR (ATR): 3272, 1647, 1543, 1467, 1246, 1225, 1028, 789, 709 cm^{-1}.

MS (EI) *m/z* (relative intensity) 464/462 (22/23) $[M]^+$, 330/298 (99/100), 220/218 (75/75), 204 (29), 121 (45).

HR-MS (EI): *m/z* calcd for $C_{25}H_{23}BrN_2O_2^+$ 462.0943, found 462.0950 $[M]^+$.

Synthesis of 2-(1,5-Dimethyl-2-phenyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (96ih):



The general procedure B was followed using 2-(1,5-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**95i**) (161 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96ih** (181 mg, 91%) as a pale white solid (m. p. = 180–181 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 1H), 7.27 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.04 (t, *J* = 6.0 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H), 3.68 (s, 2H), 3.59 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5 (C_q), 158.7 (C_q), 139.9 (C_q), 135.7 (C_q), 130.8 (C_q), 130.5 (C_q), 130.2 (CH), 129.4 (C_q), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.5 (C_q), 123.9

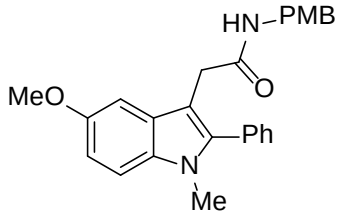
(CH), 118.5 (CH), 113.8 (CH), 109.3 (CH), 105.0 (C_q), 55.2 (CH_3), 42.7 (CH_2), 32.9 (CH_2), 31.0 (CH_3), 21.4 (CH_3).

IR (ATR): 3261, 2912, 1630, 1512, 1253, 1176, 1031, 796, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity) 398 (22) $[M]^+$, 234 (100), 218 (23), 121 (15).

HR-MS (EI): *m/z* calcd for $C_{26}H_{26}N_2O_2^+$ 398.1994, found 398.1985 $[M]^+$.

Synthesis of 2-(5-Methoxy-1-methyl-2-phenyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)-acetamide (96jh):



The general procedure B was followed using 2-(5-methoxy-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**95j**) (169 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96jh** (180 mg, 87%) as a pale white solid (m. p. = 178–179 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.29 (dd, *J* = 8.5, 7.6 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 2.3 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.10 (t, *J* = 6.0 Hz, 1H), 4.33 (d, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.69 (s, 2H), 3.60 (s, 3H).

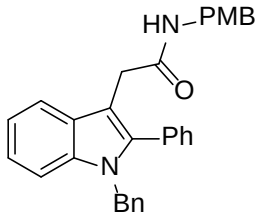
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C_q), 158.8 (C_q), 154.6 (C_q), 140.4 (C_q), 132.5 (C_q), 130.8 (C_q), 130.4 (C_q), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.6 (C_q), 113.8 (CH), 112.8 (CH), 110.5 (CH), 105.2 (C_q), 100.1 (CH), 55.8 (CH_3), 55.2 (CH_3), 42.7 (CH_2), 32.9 (CH_2), 31.1 (CH_3).

IR (ATR): 3267, 1631, 1513, 1482, 1235, 1164, 1027, 703 cm^{-1}.

MS (EI) *m/z* (relative intensity) 414 (25) $[M]^+$, 250 (100), 235 (10), 206 (17), 121 (15).

HR-MS (EI): *m/z* calcd for $C_{26}H_{26}N_2O_3^+$ 414.1943, found 414.1948 $[M]^+$.

Synthesis of 2-(1-Benzyl-2-phenyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (96kh):



The general procedure B was followed using 2-(1-benzyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**95k**) (192 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography

(*n*-hexane/EtOAc: 2/1) yielded **96kh** (198 mg, 86%) as a pale white solid (m. p. = 178–179 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.59 (m, 1H), 7.42–7.32 (m, 3H), 7.24–7.16 (m, 8H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.91–6.87 (m, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 5.97 (t, *J* = 5.8 Hz, 1H), 5.23 (s, 2H), 4.32 (d, *J* = 5.8 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 2H).

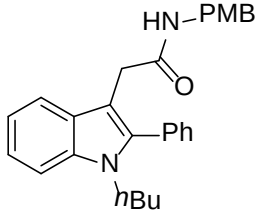
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3 (C_q), 158.8 (C_q), 140.0 (C_q), 137.8 (C_q), 136.9 (C_q), 130.6 (C_q), 130.4 (C_q), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 127.6 (C_q), 127.2 (CH), 125.9 (CH), 122.6 (CH), 120.4 (CH), 118.9 (CH), 113.9 (CH), 110.6 (CH), 106.4 (C_q), 55.2 (CH_3), 47.7 (CH_2), 42.9 (CH_2), 32.9 (CH_2).

IR (ATR): 3309, 1637, 1511, 1240, 1032, 811, 744 cm^{-1}.

MS (EI) *m/z* (relative intensity) 460 (31) $[M]^+$, 296 (100), 204 (19), 91 (89).

HR-MS (EI): *m/z* calcd for $C_{31}H_{28}N_2O_2^+$ 460.2151, found 460.2146 $[M]^+$.

Synthesis of 2-(1-*n*-Butyl-2-phenyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (96lh):



The general procedure B was followed using 2-(1-*n*-butyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**95l**) (175 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96lh** (199 mg, 93%) as a pale white solid (m. p. = 94–95 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.26 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.18 (ddd, *J* = 7.8, 7.0, 1.3 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.93 (t, *J* = 5.9 Hz, 1H), 4.29 (d, *J* = 5.9 Hz, 2H), 4.01 (t, *J* = 7.3 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 2H), 1.60 (tt, *J* = 7.3, 7.3 Hz, 2H), 1.11 (tq, *J* = 7.3, 7.3 Hz, 2H), 0.74 (t, *J* = 7.3 Hz, 3H).

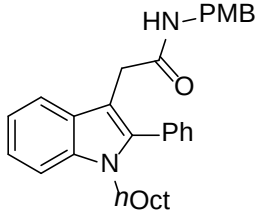
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C_q), 158.8 (C_q), 139.7 (C_q), 136.4 (C_q), 131.1 (C_q), 130.5 (C_q), 130.3 (CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 127.4 (C_q), 122.2 (CH), 120.0 (CH), 118.9 (CH), 95.8 (CH), 110.1 (CH), 105.9 (C_q), 55.3 (CH_3), 43.8 (CH_2), 42.8 (CH_2), 32.8 (CH_2), 32.0 (CH_2), 19.9 (CH_2), 13.5 (CH_3).

IR (ATR): 3300, 2954, 1629, 1511, 1233, 1030, 739, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity) 426 (54) $[M]^+$, 262 (100), 206 (25), 121 (16).

HR-MS (EI): *m/z* calcd for $C_{28}H_{30}N_2O_2^+$ 426.2307, found 426.2312 $[M]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-2-(1-*n*-octyl-2-phenyl-1*H*-indol-3-yl)acetamide (96mh):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-*n*-octyl-1*H*-indol-3-yl)acetamide (**95m**) (203 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96mh** (176 mg, 73%) as a pale white solid (m. p. = 100–101 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (dd, *J* = 7.9, 0.9 Hz), 7.49–7.42 (m, 3H), 7.38 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.29–7.23 (m, 3H), 7.18 (ddd, *J* = 7.9, 6.9, 1.2 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.95 (t, *J* = 5.9 Hz, 1H), 4.29 (d, *J* = 5.9 Hz, 2H), 3.99 (t, *J* = 7.4 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 2H), 1.62 (tt, *J* = 7.4 Hz, 2H), 1.30–1.03 (m, 10H), 0.85 (t, *J* = 7.4 Hz, 3H).

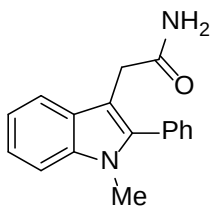
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C_q), 158.8 (C_q), 139.7 (C_q), 136.3 (C_q), 131.1 (C_q), 130.4 (C_q), 130.3 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 127.4 (C_q), 122.2 (CH), 120.0 (CH), 118.9 (CH), 113.8 (CH), 110.0 (CH), 105.8 (C_q), 55.2 (CH_3), 44.0 (CH_2), 42.8 (CH_2), 32.8 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 26.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

IR (ATR): 3285, 2922, 2850, 1644, 1545, 1354, 1254, 1174, 1027, 814, 726, 707 cm^{-1}.

MS (EI) *m/z* (relative intensity) 482 (24) $[M]^+$, 318 (100), 206 (20), 121 (23).

HR-MS (EI): *m/z* calcd for $C_{32}H_{38}N_2O_2^+$ 482.2933, found 482.2938 $[M]^+$.

Synthesis of 2-(1-Methyl-2-phenyl-1*H*-indol-3-yl)acetamide (96oh):



The general procedure B was followed using 2-(1-methyl-1*H*-indol-3-yl)acetamide (**95o**) (94 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/2) yielded **96oh** (100 mg, 76%) as a pale white solid (m. p. = 193–194 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (dd, J = 7.8, 1.2 Hz, 1H), 7.54–7.46 (m, 3H), 7.40–7.37 (m, 3H), 7.31 (ddd, J = 7.8, 6.9, 1.0 Hz, 1H), 7.21 (ddd, J = 7.5, 6.9, 1.2 Hz, 1H), 5.71 (s, 2H), 3.65 (s, 3H), 3.64 (s, 2H).

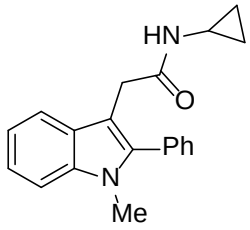
^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4 (C_q), 139.7 (C_q), 137.3 (C_q), 130.7 (C_q), 130.3 (CH), 128.7 (CH), 128.6 (CH), 127.2 (C_q), 122.4 (CH), 120.1 (CH), 118.7 (CH), 109.6 (CH), 106.1 (C_q), 32.5 (CH_2), 31.0 (CH_3).

IR (ATR): 3378, 3191, 1651, 1461, 1399, 1235, 733, 615 cm^{-1}.

MS (EI) *m/z* (relative intensity) 264 (25) $[M]^+$, 220 (100), 204 (29), 178 (10).

HR-MS (EI): *m/z* calcd for $C_{17}H_{16}N_2O^+$ 264.1263, found 264.1255 $[M]^+$.

Synthesis of *N*-Cyclopropyl-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acetamide (96ph):



The general procedure B was followed using *N*-cyclopropyl-(1-methyl-1*H*-indol-3-yl)acetamide (**113p**) (96 mg**,** 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/4) yielded **96ph** (150 mg, 98%) as a pale white solid (m. p. = 182–183 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (dd, J = 7.9, 1.0 Hz, 1H), 7.53–7.44 (m, 3H), 7.39 (dd, J = 8.2, 1.2 Hz, 1H), 7.37–7.33 (m, 2H), 7.30 (ddd, J = 8.2, 6.9, 1.0 Hz, 1H), 7.19 (ddd, J = 7.9, 6.9, 1.2 Hz, 1H), 5.83 (s, 1H), 3.65 (s, 3H), 3.63 (s, 2H), 2.61 (tt, J = 7.0, 4.0 Hz, 1H), 0.68 (ddd, J = 8.1, 7.0, 5.6 Hz, 2H), 0.29 (ddd, J = 7.6, 5.6, 4.0 Hz, 2H).

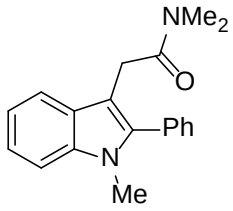
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 (C_q) , 139.7 (C_q), 137.2 (C_q), 130.7 (C_q), 130.2 (CH), 128.7 (CH), 128.6 (CH), 127.2 (C_q), 122.3 (CH), 120.1 (CH), 118.6 (CH), 109.6 (CH), 105.8 (C_q), 32.8 (CH_2), 31.0 (CH_3), 22.5 (CH), 6.5 (CH_2).

IR (ATR): 3291, 1639, 1533, 1470, 1231, 765, 737, 707 cm^{-1}.

MS (EI) *m/z* (relative intensity) 304 (23) $[M]^+$, 220 (100), 204 (27), 178 (11).

HR-MS (EI): *m/z* calcd for $C_{20}H_{20}N_2O^+$ 304.1576, found 304.1587 $[M]^+$.

Synthesis of *N*,*N*-Dimethyl-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acetamide (96qh):



The general procedure B was followed using *N*,*N*-dimethyl-(1-methyl-1*H*-indol-3-yl)acetamide (**95q**) (108 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/4) yielded **96qh** (141 mg, 96%) as a pale yellow solid (m. p. = 136–137 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.58–7.39 (m, 5H), 7.35 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 7.17 (ddd, *J* = 7.8, 6.9, 1.2 Hz, 1H), 3.77 (s, 2H), 3.62 (s, 3H), 2.89 (s, 3H), 2.77 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3 (C_q), 138.4 (C_q), 137.2 (C_q), 131.4 (C_q), 130.5 (CH), 128.4 (CH), 128.2 (CH), 127.6 (C_q), 121.8 (CH), 119.6 (CH), 119.5 (CH), 109.2 (CH), 106.5 (C_q), 37.3 (CH_3), 35.5 (CH_3), 31.0 (CH_2), 30.8 (CH_3).

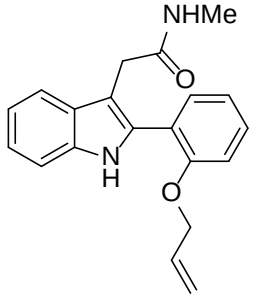
IR (ATR): 3010, 2938, 1650, 1469, 1131, 742, 713, 608 cm^{-1}.

MS (EI) *m/z* (relative intensity) 292 (20) $[M]^+$, 220 (100), 204 (25), 178 (14).

HR-MS (EI): *m/z* calcd for $C_{19}H_{20}N_2O^+$ 292.1576, found 292.1568 $[M]^+$.

Synthesis of 2-{2-[2-(Allyloxy)phenyl]-1*H*-indol-3-yl}-*N*-methylacetamide (96sp):

The general procedure B was followed using 2-(1*H*-indol-3-yl)-*N*-methylacetamide (**95s**) (47 mg, 0.25 mmol) and [2-(allyloxy)phenyl](mesityl)iodonium tosylate (**26p**) (138 mg, 0.25 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **96sp** (11 mg, 14%) as a yellow solid (m. p. = 67–69 °C), 2-iodo-1,3,5-trimethylbenzene (**108**) (7 mg, 11%) as a yellow oil and a mixture (21 mg, 30%) of 2-(allyloxy)iodobenzene (**109**) and 2-tosyloxy-1,3,5-trimethylbenzene (**110**), the ratio of which was estimated by GC to be 1:1.



^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.84 (s, 1H), 7.57 (ddd, *J* = 7.9, 0.9, 0.7 Hz, 1H), 7.42 (ddd, *J* = 8.3, 1.2, 0.7 Hz, 1H), 7.39 (ddd, *J* = 7.8, 7.6, 1.6 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.26 (ddd, *J* = 8.3, 7.0, 1.0 Hz, 1H), 7.17 (ddd, *J* = 7.9, 7.0, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.6, 1.1 Hz, 1H), 7.03 (dd, *J* = 7.8, 1.1 Hz, 1H), 5.99 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.84 (q, *J* = 4.9 Hz, 1H), 5.33 (ddt, *J* = 17.3,

3.0, 1.7 Hz, 1H), 5.26 (ddt, *J* = 10.5, 3.0, 1.5 Hz, 1H), 4.59 (ddd, *J* = 5.2, 1.7, 1.5 Hz, 2H), 3.77 (s, 2H), 2.70 (d, *J* = 4.9 Hz, 3H).

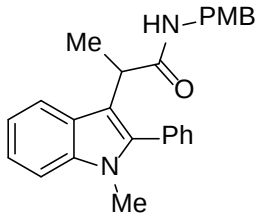
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.1 (C_q), 155.7 (C_q), 135.6 (C_q), 133.6 (C_q), 132.6 (CH), 130.9 (CH), 129.8 (CH), 128.0 (C_q), 122.5 (CH), 121.4 (CH), 120.6 (C_q), 120.0 (CH), 118.6 (CH), 117.9 (C_q), 113.0 (CH), 110.8 (CH), 106.5 (CH_2), 69.4 (CH_2), 33.2 (CH_2), 26.4 (CH_3).

IR (ATR): 3385, 2167, 2018, 1651, 1488, 1456, 1221, 993, 740 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 663 (38) $[2M+Na]^+$, 641 (40) $[2M+H]^+$, 343 (33) $[M+Na]^+$, 321 (100) $[M+H]^+$.

HR-MS (ESI): *m/z* calcd for $C_{20}H_{21}N_2O_2^+$ 321.1603, found 321.1601 $[M+H]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)propanamide (96th):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)propanamide (**95t**) (81 mg, 0.250 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 3/2) yielded **96th** (46 mg, 46%) as a yellow solid (m. p. = 137–138 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (ddd, *J* = 8.1, 1.0, 0.9 Hz, 1H), 7.51–7.45 (m, 3H), 7.36 (ddd, *J* = 8.2, 1.2, 0.9 Hz, 1H), 7.33–7.30 (m, 2H), 7.28 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.97 (t, *J* = 5.4 Hz, 1H), 4.30 (qd, *J* = 14.8, 5.4 Hz, 2H), 3.77 (s, 3H), 3.74 (t, *J* = 7.4 Hz, 1H), 3.57 (s, 3H), 1.63 (d, *J* = 7.4 Hz, 3H).

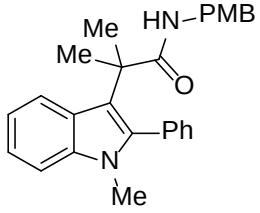
^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.3 (C_q), 158.6 (C_q), 139.0 (C_q), 137.3 (C_q), 131.0 (C_q), 130.6 (C_q), 130.4 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 125.5 (C_q), 122.0 (CH), 120.2 (CH), 119.7 (CH), 113.7 (CH), 112.1 (C_q), 109.6 (CH), 55.3 (CH_3), 43.0 (CH_2), 38.2 (CH), 30.9 (CH_3), 17.7 (CH_3).

IR (ATR): 3385, 3128, 2790, 1644, 1509, 1467, 1242, 1035, 736, 701 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 819 (50) $[2M+Na]^+$, 797 (41) $[2M+H]^+$, 421 (19) $[M+Na]^+$, 399 (100) $[M+H]^+$.

HR-MS (ESI): *m/z* calcd for $C_{26}H_{27}N_2O_2^+$ 399.2073, found 399.2059 $[M+H]^+$.

Synthesis of *N*-(4-Methoxybenzyl)-2-methyl-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)-propionamide (96uh):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-methyl-2-(1-methyl-1*H*-indol-3-yl)-propanamide (**95u**) (50 mg, 0.15 mmol) and diphenyliodonium tosylate (**26h**) (101 mg, 0.22 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **96uh** (12 mg, 20%) as a yellow solid (m. p. = 152–153 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.1 Hz, 1H), 7.49–7.41 (m, 3H), 7.32–7.28 (m, 3H), 7.25 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 7.10 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.93 (t, *J* = 5.3 Hz, 1H), 4.29 (d, *J* = 5.3 Hz, 2H), 3.76 (s, 3H), 3.34 (s, 3H), 1.41 (s, 6H).

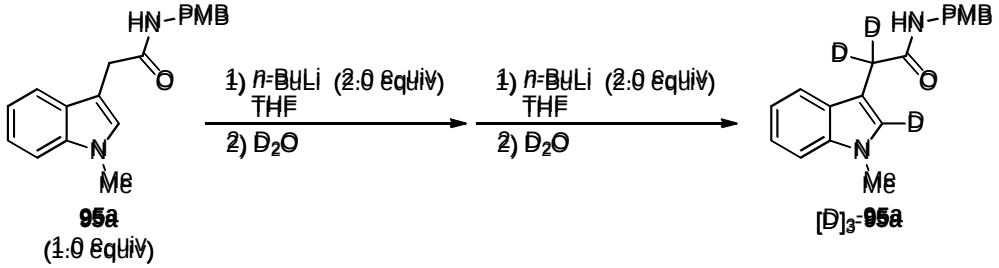
^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.3 (C_q), 158.6 (C_q), 137.8 (C_q), 136.6 (C_q), 133.7 (C_q), 131.0 (CH), 130.7 (C_q), 128.8 (CH), 128.7 (CH), 128.0 (CH), 126.0 (C_q), 121.9 (CH), 120.8 (CH), 119.5 (CH), 115.6 (C_q), 113.7 (CH), 109.3 (CH), 55.3 (CH_3), 44.1 (CH_2), 43.2 (C_q), 30.2 (CH_3), 28.5 (CH_3).

IR (ATR): 3385, 3200, 1648, 1511, 1463, 1361, 1245, 1178, 1031, 744, 723 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 847 (50) $[2M+Na]^+$, 825 (41) $[2M+H]^+$, 435 (23) $[M+Na]^+$, 413 (100) $[M+H]^+$.

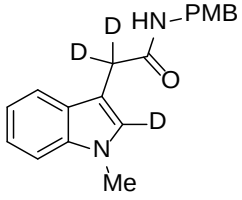
HR-MS (ESI): *m/z* calcd for $C_{27}H_{29}N_2O_2^+$ 413.2229, found 413.2227 $[M+H]^+$.

Synthesis of 2,2-*Dideutero*-*N*-(4-methoxybenzyl)-2-(2-*deutero*-1-methyl-1*H*-indol-3-yl)acetamide ([D]$_3$-95a):



A flame-dried flask was charged with *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)-acetamide (**95a**) (1.54 g, 5.0 mmol) and anhydrous THF (10 mL) under a N_2 atmosphere. The reaction was allowed to stir until all the acetamide was dissolved. The solution was cooled to

0 °C, and a 2.67 M *n*-BuLi solution in hexane (3.75 mL, 10.0 mmol) was added dropwise. The resulting solution was allowed to warm up to ambient temperature and stirred for an additional 20 minutes. Very slowly, 0.5 mL of D_2O was added dropwise. The solution was extracted with *n*-hexane (3 × 5 mL). The organic layers were combined and dried over Na_2SO_4, and the solvents were removed *in vacuo*. The resulting crude product was transferred to the flame-dried flask, and the above described deuteration procedure was repeated again. The final purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded $[D]_3$-**95a** (996 mg, 64%) as a pale white solid (m. p. = 96–97 °C).



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.30 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.24 (ddd, *J* = 8.3, 6.7, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.99 (t, *J* = 5.9 Hz, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H).

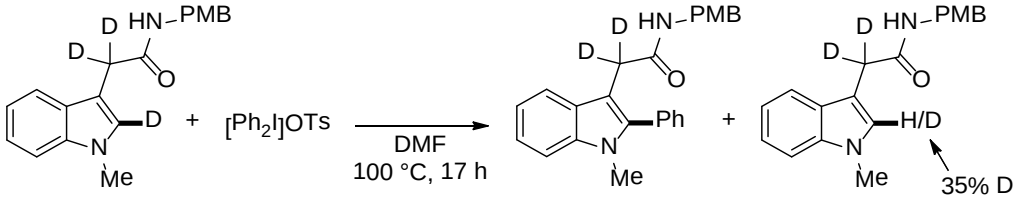
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C_q), 158.8 (C_q), 137.1 (C_q), 130.4 (C_q), 128.8 (CH), 128.0 (t, J_{C-D} = 27.8 Hz, CD), 127.5 (C_q), 122.2 (CH), 119.6 (CH), 118.9 (CH), 113.9 (CH), 109.5 (CH), 107.1 (C_q), 55.3 (CH_3), 42.8 (CH_2), 33.0 (quintet, J_{C-D} = 19.3 Hz, CD_2), 32.7 (CH_3).

IR (ATR): 3254, 2937, 1626, 1510, 1494, 1249, 1029, 747 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 623 (38) $[2M+H]^+$, 357 (16) $[M+2Na]^+$, 312 (100) $[M+H]^+$.

HR-MS (EI): *m/z* calcd for $C_{19}H_{18}D_3N_2O_2^+$ 312.1791, found 312.1789 $[M+H]^+$.

H/D-Exchange Experiment with $[D]_3$-95a:

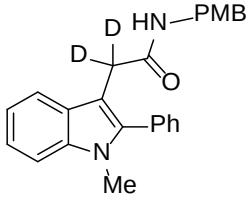


$[D]_3$-**95a** (1.0 equiv) | **26h** (0.5 equiv) | $[D]_2$-**96ah**: 78% | $[D]_n$-**95a**: 39%

A mixture of 2,2-*dideutero*-*N*-(4-methoxybenzyl)-2-(2-*deutero*-1-methyl-1*H*-indol-3-yl)-acetamide $[D]_3$-**95a** (156 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (113 mg, 0.25 mmol) in DMF (2.00 mL) was stirred at 100 °C for 17 h. At ambient temperature, H_2O

(5 mL) was added, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 2/1) yielded $[D]_2$-**96aa** (75 mg, 78% on the basis of **26a**) as a pale white solid (m. p. = 165–166 °C) and $[D]_n$-**95a** (61 mg, 39%). The deuterium incorporation was estimated by ^{1}H NMR spectroscopy.

2,2-*Dideutero*-*N*-(4-methoxybenzyl)-2-(2-*deutero*-1-methyl-2-phenyl-1*H*-indol-3-yl)-acetamide ($[D]_2$-**96ah):**



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (dd, J = 8.0, 1.0 Hz, 1H), 7.46–7.41 (m, 3H), 7.36 (dd, J = 8.2, 1.2 Hz, 1H), 7.33–7.25 (m, 3H), 7.25 (ddd, J = 8.1, 6.7, 1.3 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H), 6.00 (t, J = 5.9 Hz, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.76 (s, 3H), 3.60 (s, 3H).

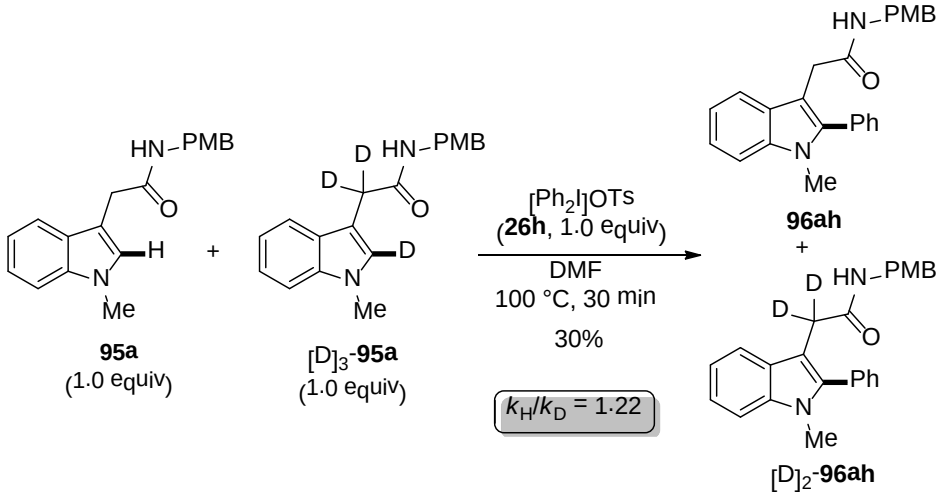
^{13}C NMR (75 MHz, $CDCl_3$): δ= 171.4(C_q), 158.7 (C_q), 139.9 (C_q), 137.3(C_q), 130.7 (C_q), 130.4 (C_q), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.3 (C_q), 122.4 (CH), 120.1 (CH), 118.8 (CH), 113.8 (CH), 109.6 (CH), 105.6 (C_q), 55.2 (CH_3), 42.8 (CH_2), 32.5 (quintet, J_{C-D} = 17.6 Hz, CD_2), 31.0 (CH_3).

IR (ATR): 3248, 2937, 1625, 1510, 1494, 1251, 1026, 747 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1181 (23) $[3M+Na]^+$, 795 (81) $[2M+Na]^+$, 409 (100) $[M+Na]^+$.

HR-MS (ESI): *m/z* calcd for $C_{25}H_{22}D_2N_2NaO_2^+$ 409.1861, found 409.1857 $[M+Na]^+$.

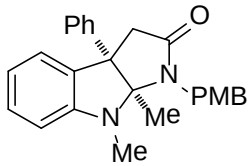
Kinetic Isotope Effect Studies by Intermolecular Competition Experiment



A mixture of *N*-(4-methoxybenzyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**95a**) (154 mg, 0.50 mmol), 2,2-*dideutero*-*N*-(4-methoxybenzyl)-2-(2-*deutero*-1-methyl-1*H*-indol-3-yl)-acetamide ([D]$_3$-**95a**) (156 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (226 mg, 0.50 mmol) in DMF (2.00 mL) was stirred at 100 °C for 30 min. At ambient temperature, H_2O (5 mL) was added, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layers were combined, and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (*n*-hexane/EtOAc: 2/1) yielded a mixture of **96ah** and [D]$_2$-**96ah** as a pale white solid (116 mg, 30%). The kinetic isotope effect of this reaction was determined to be k_H/k_D = 1.22, as estimated by ^{1}H NMR spectroscopy.

5.4.3 Analytical Data for Pyrroloindolones

Synthesis of 8,8a-Dimethyl-1-(4-methoxybenzyl)-3a-phenyl-3,3a,8,8a-tetrahydro-pyrrolo[2,3-*b*]indol-2(1*H*)-one (98ah):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97a**) (161 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98ah** (177 mg, 89%) as a pale white solid (m. p. = 145–146 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 3H), 7.16 (ddd, *J* = 7.8, 7.6, 1.3 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.8 Hz, 2H), 6.97 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.75 (ddd, *J* = 7.6, 7.5, 1.1 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.28 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.50 (d, *J* = 16.7 Hz, 1H), 3.14 (d, *J* = 16.7 Hz, 1H), 2.69 (s, 3H), 1.06 (s, 3H).

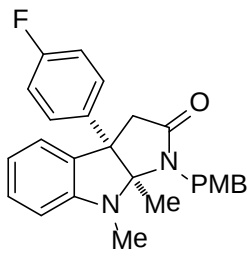
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C_q), 158.4 (C_q), 149.0 (C_q), 139.6 (C_q), 134.4 (C_q), 129.4 (C_q), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 124.2 (CH), 118.8 (CH), 113.7 (CH), 106.9 (CH), 91.5 (C_q), 58.2 (C_q), 55.2 (CH_3), 43.0 (CH_2), 39.2 (CH_2), 29.3 (CH_3), 18.4 (CH_3).

IR (ATR): 2912, 1681, 1488, 1246, 1034, 749, 701, 621 cm^{-1}.

MS (EI) *m/z* (relative intensity) 398 (39) $[M]^+$, 236 (65), 221 (76), 121 (100).

HR-MS (EI): m/z calcd for $C_{26}H_{26}N_2O_2^+$ 398.1994, found 398.1996 $[M]^+$.

Synthesis of 8,8a-Dimethyl-3a-(4-fluorophenyl)-1-(4-methoxybenzyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98ai):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97a**) (161 mg, 0.50 mmol) and bis(4-fluorophenyl)iodonium（**26i**）tosylate (366 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98ai** (168 mg, 81%) as a pale white solid (m. p. = 166–167 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (ddd, *J* = 7.6, 7,6, 1.3 Hz, 1H), 7.09–6.82 (m, 7H), 6.73 (ddd, *J* = 7.6, 7,6, 0.9 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.28 (d, *J* = 7.6 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.43 (d, *J* = 16.6 Hz, 1H), 3.13 (d, *J* = 16.6 Hz, 1H), 2.69 (s, 3H), 1.05 (s, 3H).

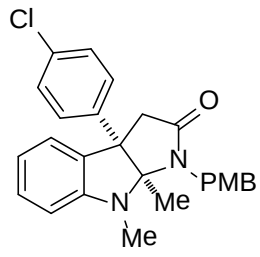
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1 (C_q), 163.4 (C_q, J_{C-F} = 245.7 Hz), 158.5 (C_q), 148.8 (C_q), 135.4 (C_q, J_{C-F} = 3.2 Hz), 134.2 (C_q), 129.3 (C_q), 129.2 (CH), 129.1 (CH, J_{C-F} = 3.2 Hz), 127.8 (CH), 124.1 (CH), 118.9 (CH), 115.2 (CH, J_{C-F} = 21.2 Hz), 113.7 (CH), 107.1 (CH), 91.4 (C_q), 57.7 (C_q), 55.2 (CH_3), 43.0 (CH_2), 39.3 (CH_2), 29.3 (CH_3), 18.4 (CH_3).

IR (ATR): 3011, 1694, 1604, 1509, 1489, 1294, 755, 519 cm^{-1}.

MS (EI) *m/z* (relative intensity) 416 (31) $[M]^+$, 254 (42), 239 (71), 121 (100).

HR-MS (EI): *m/z* calcd for $C_{26}H_{25}FN_2O_2^+$ 416.1900, found 416.1900 $[M]^+$.

Synthesis of 3a-(4-Chlorophenyl)-8,8a-dimethyl-1-(4-methoxybenzyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98aj):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97a**) (161 mg, 0.50 mmol) and bis(4-chlorophenyl)iodonium tosylate (**26j**) (391 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98aj** (179 mg, 83%) as a pale light yellow solid (m. p. = 182–183 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.6 Hz, 2H), 7.17 (ddd, *J* = 7.7, 7,7, 1.3 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.93 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.75 (ddd, *J* =

7.7, 7.7, 1.0 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.27 (d, *J* = 7.7 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.29 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.41 (d, *J* = 16.6 Hz, 1H), 3.12 (d, *J* = 16.6 Hz, 1H), 2.69 (s, 3H), 1.06 (s, 3H).

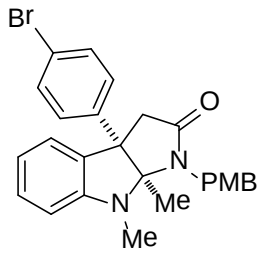
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (C_q), 158.5 (C_q), 148.8 (C_q), 138.2 (C_q), 133.9 (C_q), 133.2 (C_q), 129.3 (C_q), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.8 (CH), 124.1 (CH), 119.0 (CH), 113.7 (CH), 107.1 (CH), 91.3 (C_q), 57.8(C_q), 55.2 (CH_3), 43.0 (CH_2), 39.0 (CH_2), 29.3 (CH_3), 18.4 (CH_3).

IR (ATR): 3011, 1692, 1606, 1512, 1490, 1293, 746, 509 cm^{-1}.

MS (EI) *m/z* (relative intensity) 434/432 (7/21) $[M]^+$, 272/270 (11/33), 257/255 (17/52), 121 (100).

HR-MS (EI): *m/z* calcd for $C_{26}H_{25}ClN_2O_2^+$ 432.1605, found 432.1605 $[M]^+$.

Synthesis of 3a-(4-Bromophenyl)-8,8a-dimethyl-1-(4-methoxybenzyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98ak):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97a**) (161 mg, 0.50 mmol) and bis(4-bromophenyl)iodonium tosylate (**26k**) (458 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98ak** (188 mg, 79%) as a pale white solid (m. p. = 160–161 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.7 Hz, 2H), 7.17 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 6.98–6.89 (m, 3H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.75 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.27 (dd, *J* = 7.6, 1.0 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.29 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.41 (d, *J* = 16.5 Hz, 1H), 3.12 (d, *J* = 16.5 Hz, 1H), 2.69 (s, 3H), 1.06 (s, 3H).

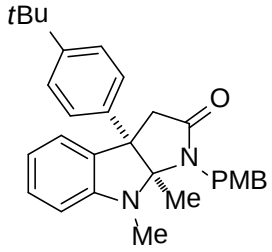
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (C_q), 158.6 (C_q), 148.9 (C_q), 138.8 (C_q), 133.9 (C_q), 131.5 (CH), 129.3 (C_q), 129.3 (CH), 129.2 (CH), 127.8 (CH), 124.1 (CH), 121.5 (C_q), 119.0 (CH), 113.8 (CH), 107.2 (CH), 91.3 (C_q), 57.9 (C_q), 55.3 (CH_3), 43.1 (CH_2), 39.0 (CH_2), 29.3 (CH_3), 18.5 (CH_3).

IR (ATR): 3060, 1691, 1606, 1511, 1488, 1294, 1244, 744 cm^{-1}.

MS (EI) *m/z* (relative intensity) 478/476 (14/14) $[M]^+$,316/314 (24/24), 301/299 (31/31), 158 (19), 121 (100).

HR-MS (EI): *m/z* calcd for $C_{26}H_{25}BrN_2O_2^+$ 476.1099, found 476.1097 $[M]^+$.

Synthesis of 3a-(4-*tert*-Butylphenyl)-8,8a-dimethyl-1-(4-methoxybenzyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98al):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97a**) (161 mg, 0.50 mmol) and bis(4-*tert*-butylphenyl)iodonium tosylate (**26l**) (423 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98al** (193 mg, 85%) as a pale white solid (m. p. = 83–85 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2H), 7.16 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 7.00–6.94 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.76 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.26 (dd, *J* = 7.6, 0.6 Hz, 1H), 4.58 (d, *J* = 16.1 Hz, 1H), 4.28 (d, *J* = 16.1 Hz, 1H), 3.76 (s, 3H), 3.48 (d, *J* = 16.6 Hz, 1H), 3.12 (d, *J* = 16.6 Hz, 1H), 2.68 (s, 3H), 1.26 (s, 9H), 1.06 (s, 3H).

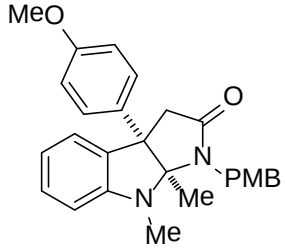
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5 (C_q), 158.5 (C_q), 150.1 (C_q), 149.0 (C_q), 136.5 (C_q), 134.5 (C_q), 129.5 (C_q), 128.8 (CH), 127.8 (CH), 127.1 (CH), 125.2 (CH), 124.3 (CH), 118.7 (CH), 113.7 (CH), 106.9 (CH), 91.5 (C_q), 57.9 (C_q), 55.2 (CH_3), 43.0 (CH_2), 39.3 (CH_2), 34.3 (C_q), 31.2 (CH_3), 29.3 (CH_3), 18.6 (CH_3).

IR (ATR): 2958, 1686, 1606, 1511, 1490, 1301, 1243, 741 cm^{-1}.

MS (EI) *m/z* (relative intensity) 454 (46) $[M]^+$, 292 (92), 277 (53), 262 (24), 121 (100).

HR-MS (EI): *m/z* calcd for $C_{30}H_{34}N_2O_2^+$ 454.2620, found 454.2608 $[M]^+$.

Synthesis of 8,8a-Dimethyl-1-(4-methoxybenzyl)-3a-(4-methoxyphenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98ag):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97a**) (161 mg, 0.50 mmol) and bis(4-methoxyphenyl)iodonium tosylate (**26g**) (384 mg, 0.75 mmol). After 17 h, purification by column

chromatography (*n*-hexane/EtOAc: 1/1) yielded **98ag** (178 mg, 83%) as a pale white solid (m. p. = 71–72 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 7.00–6.93 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.80-6.75 (m, 3H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.27 (d, *J* = 7.6 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 6H), 3.44 (d, *J* = 16.6 Hz, 1H), 3.11 (d, *J* = 16.6 Hz, 1H), 2.69 (s, 3H), 1.05 (s, 3H).

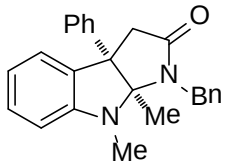
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C_q), 158.6 (C_q), 158.4 (C_q), 148.9 (C_q), 134.5 (C_q), 131.6 (C_q), 129.5 (C_q), 128.8 (CH), 128.6 (CH), 127.8 (CH), 124.1 (CH), 118.8 (CH), 113.7 (CH), 113.6 (CH), 106.9 (CH), 91.5 (C_q), 57.6 (C_q), 55.2 (CH_3), 55.1 (CH_3), 43.0 (CH_2), 39.3 (CH_2), 29.3 (CH_3), 18.4 (CH_3).

IR (ATR): 2935, 1682, 1606, 1510, 1490, 1244, 1030, 748 cm^{-1}.

MS (EI) *m/z* (relative intensity) 428 (53) $[M]^+$, 266 (100), 251 (82), 121 (90).

HR-MS (EI): *m/z* calcd for $C_{27}H_{28}N_2O_3^+$ 428.2100, found 428.2099 $[M]^+$.

Synthesis of 1-Benzyl-8,8a-dimethyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]-indol-2(1*H*)-one (98bh):



The general procedure B was followed using *N*-benzyl-2-(1,2-dimethyl-1*H*-indol-3-yl)acetamide (**97b**) (146 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98bh** (166 mg, 90%) as a pale white solid (m. p. = 68–69 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 3H), 7.21–7.11 (m, 4H), 7.06 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.01-6.88 (m, 3H), 6.76 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.24 (d, *J* = 7.4 Hz, 1H), 4.69 (d, *J* = 16.3 Hz, 1H), 4.33 (d, *J* = 16.3 Hz, 1H), 3.52 (d, *J* = 16.7 Hz, 1H), 3.16 (d, *J* = 16.7 Hz, 1H), 2.66 (s, 3H), 1.08 (s, 3H).

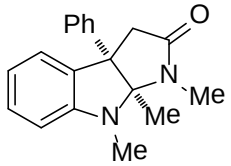
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4 (C_q), 148.9 (C_q), 139.6 (C_q), 137.2 (C_q), 134.4 (C_q), 128.9 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 126.8 (CH), 126.6 (CH), 124.2 (CH), 118.8 (CH), 107.0 (CH), 91.4 (C_q), 58.2 (C_q), 43.5 (CH_2), 39.1 (CH_2), 29.2 (CH_3), 18.4 (CH_3).

IR (ATR): 3020, 1683, 1605, 1490, 1400, 741, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity) 368 (64) $[M]^+$, 236 (61), 220 (44), 158 (20), 132 (33), 91 (100).

HR-MS (EI): *m/z* calcd for $C_{25}H_{24}N_2O^+$ 368.1889, found 368.1880 $[M]^+$.

Synthesis of 3a-Phenyl-1,8,8a-trimethyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98ch):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-methylacetamide (**97c**) (108 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98ch** (126 mg, 86%) as a pale white solid (m. p. = 190–191 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 3H), 7.18 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.7 Hz, 2H), 6.91 (dd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.72 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.51 (dd, *J* = 7.6, 1.0 Hz, 1H), 3.35 (d, *J* = 16.4 Hz, 1H), 3.00 (s, 3H), 2.96 (d, *J* = 16.4 Hz, 1H), 2.80 (s, 3H), 1.12 (s, 3H).

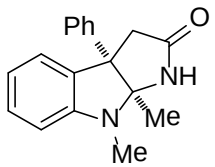
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.78 (C_q), 149.0 (C_q), 139.7 (C_q), 134.6 (C_q), 128.9 (CH), 128.4 (CH), 127.5 (CH), 127.2 (CH), 124.3 (CH), 119.0 (CH), 106.6 (CH), 90.9 (C_q), 57.7 (C_q), 39.8 (CH_2), 30.0 (CH_3), 26.6 (CH_3), 17.4 (CH_3).

IR (ATR): 2924, 1681, 1605, 1492, 1236, 1037, 740, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity) 292 (88) $[M]^+$, 234 (44), 220 (38), 158 (18), 56 (100).

HR-MS (EI): *m/z* calcd for $C_{19}H_{20}N_2O^+$ 292.1576, found 292.1583 $[M]^+$.

Synthesis of 8,8a-Dimethyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol2(1*H*)-one (98dh):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)acetamide (**97d**) (101 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98dh** (114 mg, 82%) as a pale white solid (m. p. = 206–208 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 7.30–7.20 (m, 3H), 7.19 (ddd, *J* = 7.8, 7.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 8.3, 1.8 Hz, 2H), 6.92 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.74 (ddd, *J* = 7.4,

7.0, 1.0 Hz, 1H), 6.55 (dd, *J* = 7.8, 1.0 Hz, 1H), 3.42 (d, *J* = 16.8 Hz, 1H), 2.90 (d, *J* = 16.8 Hz, 1H), 2.80 (s, 3H), 1.14 (s, 3H).

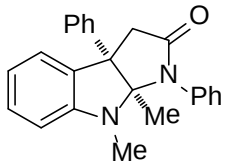
^{13}C NMR(75 MHz, $CDCl_3$):δ = 175.4 (C_q), 150.0 (C_q), 139.7 (C_q), 135.1 (C_q), 128.9 (CH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 124.3 (CH), 119.3 (CH), 108.0 (CH), 88.6 (C_q), 58.5 (C_q), 41.2 (CH_2), 28.9 (CH_3), 21.3 (CH_3).

IR (ATR): 3060, 1692, 1487, 1365, 748, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity) 278 (100) $[M]^+$, 236 (61), 234 (51), 220 (51), 194 (10), 158 (22), 118 (13).

HR-MS (EI): *m/z* calcd for $C_{18}H_{18}N_2O^+$ 278.1419, found 278.1424 $[M]^+$.

Synthesis of 8,8a-Dimethyl-1,3a-diphenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-2(1*H*)-one (98eh):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-phenylacetamide (**97e**) (139 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98eh** (94 mg, 53%) as a pale white solid (m. p. = 172–173 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 3H), 7.32–7.22 (m, 4H), 7.14–7.08 (m, 2H), 7.05–6.99 (m, 3H), 6.79 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 1H), 3.63 (d, *J* = 16.7 Hz, 1H), 3.15 (dd, *J* = 16.7 Hz, 1H), 2.44 (s, 3H), 1.28 (s, 3H).

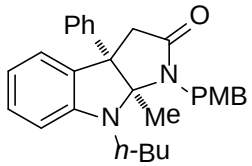
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1 (C_q), 149.0 (C_q), 139.5 (C_q), 136.6 (C_q), 134.5 (C_q), 129.7 (CH), 129.4 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 127.3 (CH), 124.5 (CH), 118.9 (CH), 106.4 (CH), 92.8 (C_q), 58.6 (C_q), 39.2 (CH_2), 29.1 (CH_3), 19.4 (CH_3).

IR (ATR): 3019, 2926, 1690, 1489, 1381, 1102, 759, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity) 354 (41) $[M]^+$, 234 (72), 220 (100), 158 (49), 118 (93), 77 (28).

HR-MS (EI): *m/z* calcd for $C_{24}H_{22}N_2O^+$ 354.1732, found 354.1724 $[M]^+$.

Synthesis of 8-*n*-Butyl-1-(4-methoxybenzyl)-8a-methyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98fh):



The general procedure B was followed using 2-(1-butyl-2-methyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97f**) (182 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/ EtOAc: 1/1) yielded **98fh** (180 mg, 82%) as a pale red solid (m. p. = 62–63 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.21 (m, 3H), 7.14 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.7 Hz, 2H), 6.97 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.75–6.70 (m, 3H), 6.26 (dd, *J* = 7.7, 1.0 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 3.51 (d, *J* = 16.4 Hz, 1H), 3.18–3.10 (m, 1H), 3.11 (d, *J* = 16.4 Hz, 1H), 2.89–2.79 (m, 1H), 1.60–1.47 (m, 1H), 1.40–1.15 (m, 3H), 1.03 (s, 3H), 0.86 (t, *J* = 7.2 Hz, 3H).

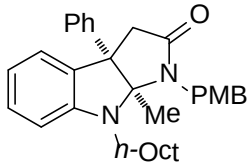
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (C_q), 158.4 (C_q), 147.9 (C_q), 139.1 (C_q), 134.6 (C_q), 129.5 (C_q), 128.7 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 127.2 (CH), 124.2 (CH), 118.5 (CH), 113.6 (CH), 107.1 (CH), 91.5 (C_q), 58.1 (C_q), 55.2 (CH_3), 42.7 (CH_2), 42.5 (CH_2), 38.5 (CH_2), 30.9 (CH_2), 20.2 (CH_2), 18.8 (CH_3), 13.8 (CH_3).

IR (ATR): 2956, 1682, 1606, 1486, 1242, 740, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity) 440 (51) $[M]^+$, 278 (79), 263 (68), 220 (40), 200 (25), 121 (100).

HR-MS (EI): *m/z* calcd for $C_{29}H_{32}N_2O_2^+$ 440.2464, found 440.2459 $[M]^+$.

Synthesis of 1-(4-Methoxybenzyl)-8a-methyl-8-octyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98gh):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(2-methyl-1-octyl-1*H*-indol-3-yl)acetamide (**97g**) (210 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98gh** (220 mg, 89%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.17 (m, 3H), 7.11 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 8.1, 1.7 Hz, 2H), 6.94 (d, *J* = 7.7, 1.3 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.75–6.65 (m,

3H), 6.23 (dd, *J* = 7.7, 0.9 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 4.32 (s, *J* = 16.0 Hz, 1H), 3.75 (s, 3H), 3.49 (d, *J* = 16.5 Hz, 1H), 3.15 (d, *J* = 16.5 Hz, 1H), 3.13–3.05 (m, 1H), 2.88–2.78 (m, 1H), 1.55–1.45 (m, 2H), 1.36–1.12 (m, 10H), 1.01 (s, 3H), 0.84 (t, *J* = 7.0 Hz, 3H).

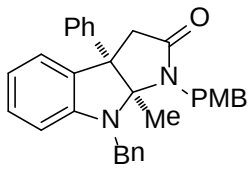
^{13}C NMR (75 MHz, $CDCl_3$): δ= 172.0 (C_q), 158.5 (C_q), 147.9 (C_q), 139.2 (C_q), 134.7 (C_q), 129.6 (C_q), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 124.4 (CH), 118.6 (CH), 113.7 (CH), 107.2 (CH), 91.5 (C_q), 58.1 (C_q), 55.3 (CH_3), 43.0 (CH_2), 42.6 (CH_2), 38.5 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 22.6 (CH_2), 18.8 (CH_3), 14.1 (CH_3).

IR (ATR): 2925, 2854, 1686, 1606, 1511, 1486, 1242, 740, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity) 496 (42) $[M]^+$, 334 (62), 319 (55), 256 (33), 220 (32), 121 (100).

HR-MS (EI): *m/z* calcd for $C_{33}H_{40}N_2O_2^+$ 496.3090, found 496.3090 $[M]^+$.

Synthesis of 8-Benzyl-1-(4-methoxybenzyl)-8a-methyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98hh):



The general procedure B was followed using 2-(1-benzyl-2-methyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97h**) (199 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98hh** (125 mg, 53%) as a pale white solid (m. p. = 166–167 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.18 (m, 6H), 7.12–7.08 (m, 4H), 7.03 (d, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.77 (dd, *J* = 4.8, 2.5 Hz, 1H), 6.72–6.68 (m, 2H), 6.10 (d, *J* = 7.6 Hz, 1H), 4.57 (d, *J* = 16.1 Hz, 1H), 4.42 (d, *J* = 16.5 Hz, 1H), 4.35 (d, *J* = 16.1 Hz, 1H), 3.84 (d, *J* = 16.5 Hz, 1H), 3.74 (s, 3H), 3.55 (d, *J* = 16.7 Hz, 1H), 3.18 (d, *J* = 16.7 Hz, 1H), 1.10 (s, 3H).

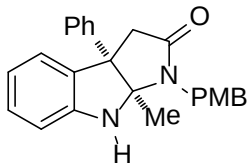
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5 (C_q), 158.5 (C_q), 148.2 (C_q), 139.0 (C_q), 138.6 (C_q), 134.0 (C_q), 129.3 (C_q), 128.8 (CH), 128.4 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 124.4 (CH), 119.2 (CH), 113.8 (CH), 108.1 (CH), 92.0 (C_q), 58.3 (C_q), 55.2 (CH_3), 47.2 (CH_2), 42.9 (CH_2), 39.52 (CH_2), 19.2 (CH_3).

IR (ATR): 3011, 1668, 1501, 1486, 1244, 1030, 739, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity) 474 (41) $[M]^+$, 312 (40), 297 (44), 207 (25), 121 (100), 91 (64).

HR-MS (EI): *m/z* calcd for $C_{32}H_{30}N_2O_2^+$ 474.2307, found 474.2315 $[M]^+$.

Synthesis of 1-(4-Methoxybenzyl)-8a-methyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo-[2,3-*b*]indol-2(1*H*)-one (98ih):



The general procedure B was followed using *N*-(4-methoxybenzyl)-2-(2-methyl-1*H*-indol-3-yl)acetamide (**97i**) (154 mg, 0.50 mmol) and diphenyliodonium tosylate (**26h**) (339 mg, 0.75 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98ih** (161 mg, 84%) as a pale white solid (m. p. = 200–201 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 3H), 7.08–7.04 (m, 5H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 7.8,7.6 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.31 (d, *J* = 7.7 Hz, 1H), 4.78 (d, *J* = 15.5 Hz, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 3.77 (s, 3H), 3.46 (d, *J* = 16.6 Hz, 1H), 3.05 (d, *J* = 16.6 Hz, 1H), 1.07 (s, 3H).

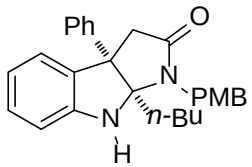
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1 (C_q), 158.8 (C_q), 147.0 (C_q), 139.6 (C_q), 135.9 (C_q), 129.8 (C_q), 128.6 (CH), 128.6 (CH), 128.4 (CH), 127.5 (CH), 127.3 (CH), 124.8 (CH), 120.6 (CH), 114.0 (CH), 110.7 (CH), 89.3 (C_q), 58.1 (C_q), 55.3 (CH_3), 42.2 (CH_2), 39.9 (CH_2), 21.4 (CH_3).

IR (ATR): 3301, 2934, 1671, 1512, 1245, 1033, 751, 504 cm^{-1}.

MS (EI) *m/z* (relative intensity) 384 (22) $[M]^+$, 222 (20), 207 (100), 121 (79).

HR-MS (EI): *m/z* calcd for $C_{25}H_{24}N_2O_2^+$ 384.1838, found 384.1839 $[M]^+$.

Synthesis of 8a-*n*-Butyl-1-(4-methoxybenzyl)-3a-phenyl-3,3a,8,8a-tetrahydro-pyrrolo-[2,3-*b*]indol-2(1*H*)-one (98jh):



The general procedure B was followed using 2-(2-*n*-butyl-1*H*-indol-3-yl)-*N*-(4-methoxybenzyl)acetamide (**97j**) (98 mg, 0.28 mmol) and diphenyliodonium tosylate (**26h**) (190 mg, 0.42 mmol). After 17 h, purification by column chromatography (*n*-hexane/ EtOAc: 4/1) yielded **98jh** (64 mg, 54%) as a pale white solid (m. p. = 181–183 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (dd, *J* = 7.2, 6.9 Hz, 2H), 7.21 (dd, *J* = 6.9, 6.9 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 7.01 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 6.86 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 2H), 6.71 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.23 (dd, *J* = 7.5, 1.2 Hz, 1H), 4.92 (d, *J* = 15.4 Hz, 1H), 4.05 (d, *J* = 15.4 Hz, 1H), 4.03 (s, 1H), 3.79 (s, 3H), 3.50 (d, *J* = 16.3 Hz, 1H), 3.03 (d, *J* = 16.3 Hz, 1H), 1.78 (dt, *J* = 14.4, 7.3 Hz, 1H), 1.65 (dt, *J* = 14.4, 7.3 Hz, 1H), 0.99–0.77 (m, 4H), 0.56 (t, *J* = 7.1 Hz, 3H).

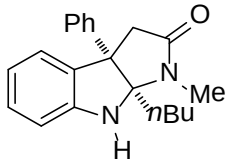
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.4 (C_q), 158.8 (C_q), 146.3 (C_q), 139.4 (C_q), 137.8 (C_q), 129.5 (C_q), 128.7 (CH), 128.2 (CH), 128.2 (CH), 127.1 (CH), 127.0 (CH), 123.9 (CH), 120.3 (CH), 113.9 (CH), 110.50 (CH), 91.8 (C_q), 57.6 (C_q), 55.3 (CH_3), 42.3 (CH_2), 39.5 (CH_2), 33.2 (CH_2), 24.6 (CH_2), 22.3 (CH_2), 13.4 (CH_3).

IR (ATR): 3329, 2952, 1660, 1610, 1511, 1248, 1028, 750 cm^{-1}.

MS (EI) *m/z* (relative intensity) 426 (14) $[M]^+$, 249 (100), 206 (36), 121 (76).

HR-MS (EI): *m/z* calcd for $C_{28}H_{30}N_2O_2^+$ 426.2307, found 426.2316 $[M]^+$.

Synthesis of 8a-*n*-Butyl-1-methyl-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (98kh):



The general procedure B was followed using 2-(2-*n*-butyl-1*H*-indol-3-yl)-*N*-methylacetamide (**97k**) (61 mg, 0.25 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98kh** (47 mg, 59%) as a pale white solid (m. p. = 76–78 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 7.2, 6.9 Hz, 2H), 7.23 (dd, *J* = 6.9, 6.9 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.09 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.86 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.75 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H), 6.71 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.53 (s, 1H), 3.48 (d, *J* = 16.3 Hz, 1H), 2.91 (d, *J* = 16.3 Hz, 1H), 2.77 (s, 3H), 1.78–1.67 (m, 1H), 1.66–1.55 (m, 1H), 1.11–0.97 (m, 1H), 0.97–0.84 (m, 3H), 0.60 (t, *J* = 6.9 Hz, 3H).

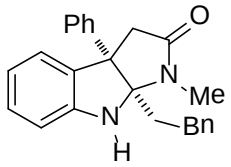
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.8 (C_q), 146.3 (C_q), 139.5 (C_q), 138.1 (C_q), 128.5 (CH), 128.2 (CH), 127.1 (CH), 127.1 (CH), 124.3 (CH), 120.6 (CH), 110.4 (CH), 90.6 (C_q), 57.8 (C_q), 39.8 (CH_2), 32.7 (CH_2), 24.8 (CH_2), 24.5 (CH_3), 22.4 (CH_2), 13.4 (CH_3).

IR (ATR): 3302, 2930, 1665, 1607, 1483, 1254, 1122, 742 cm^{-1}.

MS (EI) *m/z* (relative intensity) 320 (28) $[M]^+$, 277 (11), 263 (11), 206 (27), 98 (100).

HR-MS (EI): m/z calcd for $C_{21}H_{24}N_2O^+$ 320.1889, found 320.1896 $[M]^+$.

Synthesis of 1-Methyl-3a-phenyl-8a-phenylethyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]-indol-2(1*H*)-one (98lh):



The general procedure B was followed using *N*-methyl-2-(2-phenylethyl-1*H*-indol-3-yl)acetamide (**97l**) (73 mg, 0.25 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **98lh** (61 mg, 66%) as a pale white solid (m. p. = 208–210 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 7.2, 6.9 Hz, 2H), 7.32 (dd, *J* = 6.9, 6.9 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.18–7.08 (m, 4H), 6.90 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.79 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.75 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.64 (dd, *J* = 7.8, 1.5 Hz, 2H), 3.59 (d, *J* = 16.4 Hz, 1H), 3.04 (d, *J* = 16.4 Hz, 1H), 2.86 (s, 3H), 2.28 (dt, *J* = 12.6, 4.8 Hz, 1H), 2.14 (td, *J* = 12.6, 4.8 Hz, 1H), 2.05 (ddd, *J* = 14.6, 12.4, 4.9 Hz, 1H), 1.97 (ddd, *J* = 14.6, 12.4, 4.9 Hz, 1H).

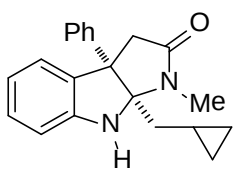
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.7 (C_q), 146.0 (C_q), 140.3 (C_q), 139.4 (C_q), 137.9 (C_q), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.0 (CH), 124.4 (CH), 120.9 (CH), 110.6 (CH), 90.2 (C_q), 57.9 (C_q), 39.9 (CH_2), 35.6 (CH_2), 29.5 (CH_2), 24.5 (CH_3).

IR (ATR): 3364, 2940, 1667, 1605, 1482, 1116, 751, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity) 368 (39) $[M]^+$, 263 (12), 206 (23), 146 (100), 118 (10), 105 (16), 91 (21).

HR-MS (EI): *m/z* calcd for $C_{25}H_{24}N_2O^+$ 368.1889, found 368.1893 $[M]^+$.

Synthesis of 8a-(Cyclopropylmethyl)-1-methyl-3a-phenyl-3,3a,8,8a-tetrahydro-pyrrolo-[2,3-*b*]indol-2(1*H*)-one (98mh):



The general procedure B was followed using 2-[2-(cyclopropylmethyl)-1*H*-indol-3-yl]-*N*-methylacetamide (**97m**) (51 mg, 0.21 mmol) and diphenyliodonium tosylate (**26h**) (145 mg, 0.32 mmol). After 17 h, purification by column chromatography (*n*-hexane/ EtOAc: 1/1)

yielded **98mh** (34 mg, 51%) as a pale white solid (m. p. = 91–93 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.34 (m, 5H), 7.23 (dd, *J* =7.5, 1.0 Hz, 1H), 7.13 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.81 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 6.73 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.78 (s, 1H), 2.98 (d, *J* = 15.2 Hz, 1H), 2.70 (d, *J* = 15.2 Hz, 1H), 2.60 (s, 3H), 1.36–1.28 (m, 1H), 0.62–0.48 (m, 1H), 0.39–0.26 (m, 1H), –0.12 to –0.20 (m, 1H), –0.24 to –0.35 (m, 1H).

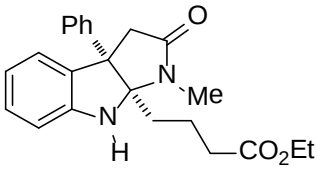
^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.2 (C_q), 146.2 (C_q), 136.5 (C_q), 132.9 (C_q), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 125.4 (CH), 119.3 (CH), 109.5 (CH), 93.2 (C_q), 55.6 (C_q), 41.2 (CH_2), 40.7 (CH_2), 24.7 (CH_3), 6.6 (CH), 5.0 (CH_2), 4.2 (CH_2).

IR (ATR): 3280, 2905, 1666, 1472, 1380, 1253, 743 cm^{-1}.

MS (EI) *m/z* (relative intensity) 318 (26) $[M]^+$, 263.2 (10), 206 (18), 118 (100), 77 (12).

HR-MS (EI): *m/z* calcd for $C_{21}H_{22}N_2O^+$ 318.1732, found 318.1736 $[M]^+$.

Synthesis of Ethyl 4-{1-Methyl-2-oxo-3a-phenyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]-indol-8a(1*H*)-yl}butanoate (98nh):



The general procedure B was followed using ethyl 4-{(3-[2-(methylamino)-2-oxoethyl]-1*H*-indol-2-yl)butanoate (**97n**) (76 mg, 0.25 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/ EtOAc: 1/1) yielded **98nh** (52 mg, 55%) as a pale white solid (m. p. = 128–130 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 3H), 7.17 (dd, *J* = 6.6, 1.7 Hz, 2H), 7.10 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 6.86 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.77 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.72 (dd, *J* = 7.6, 1.3 Hz, 1H), 4.47 (s, 1H), 4.01 (dt, *J* = 7.0, 2.6 Hz, 2H), 3.47 (d, *J* = 16.4 Hz, 1H), 2.96 (d, *J* = 16.4 Hz, 1H), 2.80 (s, 3H), 1.97 (dt, *J* = 9.2, 7.0 Hz, 1H), 1.90 (dt, *J* = 9.2, 7.0 Hz, 1H), 1.83 (ddd, *J* = 14.5, 9.4, 5.7 Hz, 1H), 1.60 (ddd, *J* = 14.5, 9.4, 5.7 Hz, 1H), 1.31–1.21 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

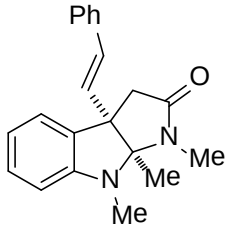
^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5 (C_q), 171.6 (C_q), 146.2 (C_q), 139.4 (C_q), 137.8 (C_q), 128.6 (CH), 128.4 (CH), 127.3 (CH), 127.1 (CH), 124.4 (CH), 120.8 (CH), 110.4 (CH), 90.2 (C_q), 60.4 (CH_2), 57.8 (C_q), 39.9 (CH_2), 33.7 (CH_2), 32.6 (CH_2), 24.4 (CH_3), 18.4 (CH_2), 14.2 (CH_3).

IR (ATR): 3266, 2962, 1726, 1655, 1483, 1178, 1148, 743 cm^{-1}.

MS (EI) *m/z* (relative intensity) 378 (42) $[M]^+$, 333 (12), 263 (18), 206 (31), 156 (100), 115 (12).

HR-MS (EI): *m/z* calcd for $C_{23}H_{26}N_2O_3^+$ 378.1943, found 378.1946 $[M]^+$.

Synthesis of (*E*)-3a-Styryl-1,8,8a-trimethyl-3,3a,8,8a-tetrahydropyrrolo-[2,3-b]-indol-2(1*H*)-one (98cq):



The general procedure B was followed using 2-(1,2-dimethyl-1*H*-indol-3-yl)-*N*-methylacetamide (**97c**) (43 mg, 0.2 mmol) and (phenyl)(styryl)iodonium triflate (**26q**) (137 mg, 0.3 mmol). After 17 h, purification by column chromatography (*n*-hexane/ EtOAc: 1/2) yielded **98cq** (40 mg, 63%) as a pale white solid (m. p. = 71–73 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5H), 7.16 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.03 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.75 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H), 6.46 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.22 (d, *J* = 16.4 Hz, 1H), 6.17 (d, *J* = 16.4 Hz, 1H), 3.01 (s, 3H), 2.91 (s, 2H), 2.77 (s, 3H), 1.49 (s, 3H).

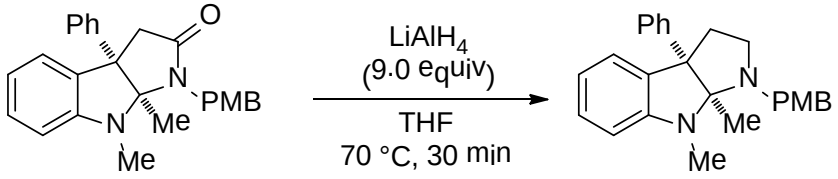
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3 (C_q), 148.5 (C_q), 136.4 (C_q), 131.3 (C_q), 131.0 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 127.7 (CH), 126.3 (CH), 124.5 (CH), 118.6 (CH), 106.5 (CH), 90.1 (C_q), 55.8 (C_q), 40.1 (CH_2) , 30.0 (CH_3), 26.4 (CH_3), 17.1 (CH_3).

IR (ATR): 2924, 1680, 1489, 1232, 741, 693 cm^{-1}.

MS (EI) *m/z* (relative intensity) 318 (34) $[M]^+$, 292 (9), 246 (9), 158 (21), 56 (100).

HR-MS (EI): *m/z* calcd for $C_{21}H_{22}N_2O^+$ 318.1732, found 318.1732 $[M]^+$.

Synthesis of 8,8a-Dimethyl-1-(4-methoxybenzyl)-3a-phenyl-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole (117ah):



98ah **117ah**: 88%

A mixture of 8,8a-dimethyl-1-(4-methoxybenzyl)-3a-phenyl-3,3a,8,8a-tetrahydropyrrolo-[2,3-*b*]indol-2(1*H*)-one (**98ah**) (80 mg, 0.2 mmol) and $LiAlH_4$ (68 mg, 1.8 mmol) in anhydrous THF (12.0 mL) was stirred at 65 °C under N_2 for 30 min. After cooling to 0 °C,

excess of EtOAc was carefully added dropwise to quench the reaction. At ambient temperature, the reaction mixture was washed with brine (10 mL), and the aqueous layer was extracted with EtOAc (2 × 100 mL). The organic layers were combined, and the solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) to yield **117ah** (68 mg, 88%) as a red oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 7H), 7.16 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.92–6.84 (m, 3H), 6.66 (dd, *J* = 7.1, 7.4 Hz, 1H), 6.45 (d, *J* = 7.4 Hz, 1H), 4.13 (d, *J* = 12.9 Hz, 1H), 3.81 (s, 3H), 3.43 (d, *J* = 12.9 Hz, 1H), 2.92 (s, 3H), 2.86 (dd, *J* = 11.8, 8.7 Hz, 1H), 2.75 (dd, *J* = 17.6, 10.2 Hz, 1H), 2.49 (ddd, *J* = 10.2, 8.7, 5.7 Hz, 1H), 2.10 (dd, *J* = 11.8, 5.7 Hz, 1H), 0.96 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5 (C_q), 152.3 (C_q), 143.8 (C_q), 134.6 (C_q), 132.6 (C_q), 129.3 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 126.3 (CH), 124.5 (CH), 116.9 (CH), 113.6 (CH), 104.9 (CH), 93.1 (C_q), 64.1 (C_q), 55.3 (CH_3), 52.4 (CH_2), 49.3 (CH_2), 37.9 (CH_2), 31.5 (CH_3), 19.7 (CH_3).

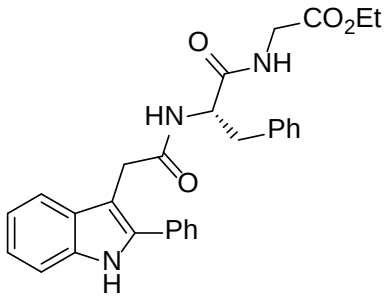
IR (ATR): 2931, 1601, 1510, 1242, 1032, 742 cm^{-1}.

MS (EI) *m/z* (relative intensity) 384 (49) $[M]^+$, 263 (10), 221 (100), 163 (22), 135 (21), 121 (84), 77 (18).

HR-MS (EI): *m/z* calcd for $C_{26}H_{28}N_2O^+$ 384.2202, found 384.2219 $[M]^+$.

5.4.4 Analytical Data for Arylated Peptide-Containing Indolylacetamides

Synthesis of Ethyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (100ah):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanylglycinate (**99a**) (102 mg, 0.250 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **100ah** (101 mg, 83%) as a pale white solid (m. p. = 220–221 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.18 (s, 1H), 8.47 (t, *J* = 5.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.48 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* =7.8, 7.8 Hz, 2H), 7.27 (d, *J* = 6.9 Hz, 2H), 7.24 (dd, *J* = 7.4, 7.2 Hz,

2H),7.22–7.18 (m, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 6.94 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 4.61 (ddd, *J* = 9.9, 8.4, 4.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.92 (dd, *J* = 17.5, 5.8 Hz, 1H), 3.84 (dd, *J* = 17.5, 5.8 Hz, 1H), 3.66 (d, *J* = 15.8 Hz, 1H), 3.60 (d, *J* = 15.8 Hz, 1H), 3.07 (dd, *J* = 13.9, 4.1 Hz, 1H), 2.83 (dd, *J* = 13.9, 9.9 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).

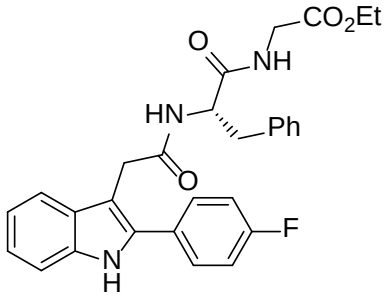
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.8 (C_q), 170.6 (C_q), 169.6(C_q), 137.7 (C_q), 135.8 (C_q), 135.8(C_q), 132.4 (C_q), 129.1(CH), 128.7 (C_q), 128.5 (CH), 128.0 (CH), 128.0 (CH), 127.4 (CH), 126.2 (CH), 121.4 (CH), 119.0 (CH), 118.6 (CH), 110.8 (CH), 105.7 (C_q), 60.4(CH_2), 54.8(CH_2), 53.8 (CH), 37.6 (CH_2), 31.5 (CH_2), 14.0 (CH_3).

IR (ATR): 3375, 3283, 1735, 1642, 1528, 1335, 1026, 772, 745, 699 cm^{-1}.

MS (EI) *m/z* (relative intensity) 483 (12) $[M]^+$, 223 (51), 206 (100), 179 (18).

HR-MS (EI): *m/z* calcd for $C_{29}H_{29}N_3O_4^+$ 483.2158, found 483.2152 $[M]^+$.

Synthesis of Ethyl {2-[2-(4-Fluorophenyl)-1H-indol-3-yl]acetyl}-*L*-phenylalanyl-glycinate (100ai):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (**99a**) (102 mg, 0.250 mmol) and bis(4-fluorophenyl)iodonium tosylate (**26i**) (183 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 3/2) yielded **100ai** (89 mg, 71%) as a light brown solid (m. p. = 218–220 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.21 (s, 1H), 8.50 (t, *J* = 5.8 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.78 (ddd, *J* = 8.5, 5.3, 2.5 Hz, 2H), 7.40–7.17 (m, 9H),7.11 (ddd, *J*= 8.0, 7.0, 1.2 Hz, 1H), 6.96 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 4.65 (ddd, *J* = 9.8, 8.4, 4.1 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.93 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.87 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.65 (d, *J* = 15.8 Hz, 1H), 3.59 (d, *J* = 15.8 Hz, 1H), 3.11 (dd, *J* = 13.9, 4.1 Hz, 1H), 2.87 (dd, *J* = 13.9, 9.8 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.6 (C_q), 170.4 (C_q), 169.4 (C_q), 161.4 (d, J_{C-F} = 244.9 Hz, C_q), 137.6 (C_q), 135.6 (C_q), 134.7 (C_q), 129.8 (d, J_{C-F} = 8.0 Hz, CH), 129.0 (CH), 128.8 (d, J_{C-F} = 3.0 Hz, C_q), 128.5 (C_q), 127.8 (CH), 126.0 (CH), 121.3 (CH), 118.9 (CH),

118.6 (CH), 115.3 (d, J_{C-F} = 21.3 Hz, CH), 110.7 (CH), 105.7 (C_q), 60.3 (CH_2), 53.8 (CH), 40.7 (CH_2), 37.6 (CH_2), 31.4 (CH_2), 14.0 (CH_3).

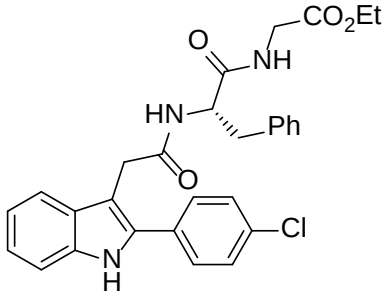
^{19}F NMR (283 MHz, d_6-DMSO):δ = –109.8 (dd, *J* = 9.2, 4.9 Hz).

IR (ATR): 3394, 3271, 3066, 1744, 1646, 1502, 1199, 1045, 841, 744, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1025 (15) $[2M+Na]^+$, 524 (30) $[M+Na]^+$.

HR-MS (ESI): *m/z* calcd for $C_{29}H_{29}FN_3O_4^+$ 502.2142, found 502.2144 $[M+H]^+$.

Synthesis of Ethyl {2-[2-(4-Chlorophenyl)-1*H*-indol-3-yl]acetyl}-*L*-phenylalanyl-glycinate (100aj):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (**99a**) (102 mg, 0.250 mmol) and bis(4-chlorophenyl)iodonium tosylate (**26j**) (196 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1→1/1) yielded **100aj** (81 mg, 63%) as a light brown solid (m. p. = 240–242 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.23 (s, 1H), 8.48 (t, *J* = 5.9 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.77–7.70 (m, 2H), 7.54–7.47 (m, 2H), 7.36 (dd, *J* = 14.1, 8.0 Hz, 2H), 7.31–7.17 (m, 5H), 7.10 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 6.94 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 4.62 (ddd, *J* = 10.0, 8.7, 4.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.91 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.85 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.65 (d, *J* = 15.6 Hz, 1H), 3.58 (d, *J* = 15.6 Hz, 1H), 3.08 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.85 (dd, *J* = 13.8, 10.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

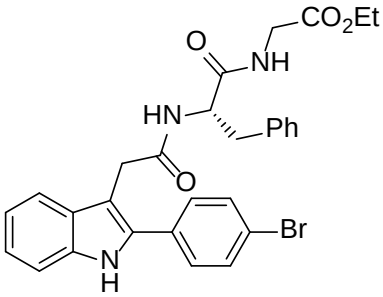
^{13}C NMR(126 MHz, d_6-DMSO): δ = 171.6 (C_q), 170.3 (C_q), 169.4 (C_q), 137.6 (C_q), 135.7 (C_q), 134.3 (C_q), 131.9 (C_q), 131.1 (C_q), 129.4 (CH), 129.0 (CH), 128.6 (C_q), 128.4 (CH), 127.8 (CH), 126.0 (CH), 121.6 (CH), 119.0 (CH), 118.6 (CH), 110.8 (CH), 106.3 (C_q), 60.3 (CH_2), 53.8 (CH), 40.7 (CH_2), 37.6 (CH_2), 31.4 (CH_2), 14.0 (CH_3).

IR (ATR): 3401, 3260, 3263, 1746, 1645, 1515, 1197, 1092, 1012, 834, 627 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1061/1059/1057 (9/54/84) $[2M+Na]^+$, 542/540 (32/100) $[M+Na]^+$.

HR-MS (ESI): *m/z* calcd for $C_{29}H_{29}ClN_3O_4^+$ 518.1847, found 518.1860 $[M+H]^+$.

Synthesis of Ethyl {2-[2-(4-Bromophenyl)-1H-indol-3-yl]acetyl}-*L*-phenylalanylglycinate (100ak):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (**99a**) 102 mg, 0.250 mmol) and bis(4-bromphenyl)iodonium tosylate (**26k**) (229 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 3/2) yielded **100ak** (86 mg, 61%) as a light brown solid (m. p. = 244–247 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.23 (s, 1H), 8.46 (t, *J* = 5.9 Hz, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 8.8, 1.7 Hz, 2H), 7.63 (dd, *J* = 8.8, 1.7 Hz, 2H), 7.35 (dd, *J* = 13.1, 8.0 Hz, 2H), 7.30–7.17 (m, 5H), 7.10 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.93 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 4.61 (ddd, *J* = 10.0, 8.6, 4.2 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.84 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.63 (d, *J* = 15.7 Hz, 1H), 3.57 (d, *J* = 15.7 Hz, 1H), 3.07 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.83 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

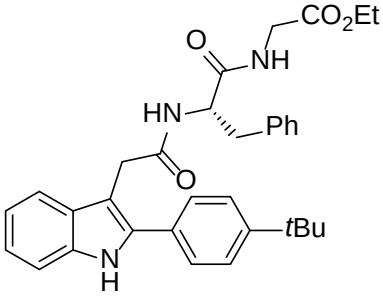
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.6 (C_q), 170.3 (C_q), 169.4 (C_q), 137.6 (C_q), 135.7 (C_q), 134.3 (C_q), 131.5 (C_q), 131.3 (CH), 129.7 (CH), 128.9 (CH), 128.6 (C_q), 127.8 (CH), 126.0 (CH), 121.6 (CH), 120.5 (C_q), 119.0 (CH), 118.6 (CH), 110.8 (CH), 106.3 (C_q), 60.3 (CH_2), 53.8 (CH), 40.7 (CH_2), 37.6 (CH_2), 31.4 (CH_2), 14.0 (CH_3).

IR (ATR): 3310, 3060, 1741, 1646, 1527, 1203, 1007, 829, 735 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1149/1147/1145 (22/44/22) $[2M+Na]^+$, 586/584 (100/100) $[M+Na]^+$.

HR-MS (ESI): *m/z* calcd for $C_{29}H_{29}BrN_3O_4^+$ 562.1336, found 562.1331 $[M+H]^+$.

Synthesis of Ethyl (2-{2-[4-(*tert*-Butyl)phenyl]-1H-indol-3-yl}acetyl)-*L*-phenylalanyl-glycinate (100al):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (**99a**) (102 mg, 0.250 mmol) and bis(4-*tert*-butylphenyl)-iodonium tosylate (**26l**) (212 mg, 0.375 mmol). After 17 h,

purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **100al** (117 mg, 87%) as a pale white solid (m. p. =223–225 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.09 (s, 1H), 8.45 (t, *J* = 5.9 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.26–7.23 (m, 2H), 7.22–7.18 (m, 1H), 7.07 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.92 (dd, *J* = 7.9, 7.0 Hz, 1H), 4.64 (ddd, *J* = 9.4, 8.5, 4.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.91 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.83 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.61 (d, *J* = 15.9 Hz, 1H), 3.58 (d, *J* = 15.9 Hz, 1H), 3.08 (dd, *J* = 13.9, 4.1 Hz, 1H), 2.84 (dd, *J* = 13.9, 9.4 Hz, 1H), 1.34 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H).

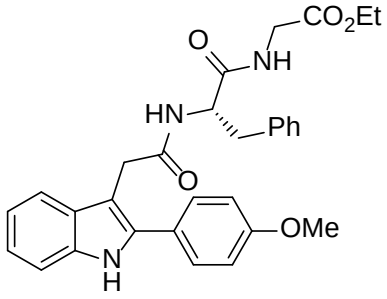
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.6 (C_q), 170.4 (C_q), 169.4 (C_q), 149.6 (C_q), 137.6 (C_q), 135.7 (C_q), 135.5 (C_q), 129.4 (C_q), 128.9 (CH), 128.7 (C_q), 127.8 (CH), 127.5 (CH), 126.0 (CH), 125.1 (CH), 121.1 (CH), 118.7 (CH), 118.4 (CH), 110.6 (CH), 105.2 (C_q), 60.3 (CH_2), 53.7 (CH), 40.7 (CH_2), 37.6 (CH_2), 34.2 (CH_2), 31.6 (C_q), 31.0 (CH_3), 14.0 (CH_3).

IR (ATR): 3265, 2960, 1749, 1647, 1569, 1511, 1191, 1095, 739 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1101 (28) $[2M+Na]^+$, 562 (100) $[M+Na]^+$, 540 (20) $[M+H]^+$.

HR-MS (ESI): *m/z* calcd for $C_{33}H_{36}N_3O_4^+$ 538.2700, found 538.2706 $[M–H]^+$.

Synthesis of Ethyl {2-[2-(4-Methoxyphenyl)-1*H*-indol-3-yl]acetyl}-*L*-phenylalanyl-glycinate (100ag):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (**99a**) (102 mg, 0.250 mmol) and bis(4-methoxyphenyl)-iodonium tosylate (**26g**) (192 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **100ag** (96 mg, 75%) as a light brown solid (m. p. =199–202 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.06 (s, 1H), 8.46 (t, *J* = 5.9 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.35–7.14 (m, 7H),7.05 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.02 (d,*J* = 8.6 Hz, 2H), 6.91 (dd, *J* = 7.9, 7.0 Hz, 1H), 4.62 (ddd, *J* = 9.4, 8.4, 4.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.83 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.81 (s, 3H),

3.60 (d, *J* = 15.8 Hz, 1H), 3.54 (d, *J* = 15.8 Hz, 1H), 3.07 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.83 (dd, *J* = 13.8, 9.4 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

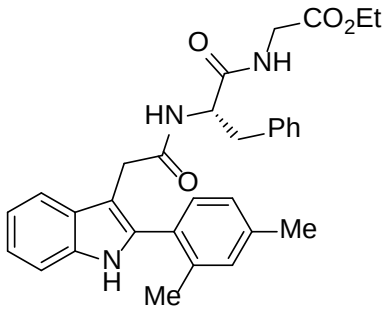
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.6 (C_q), 170.5 (C_q), 169.4 (C_q), 158.6 (C_q), 137.6 (C_q), 135.7 (C_q), 135.4 (C_q), 129.1 (CH), 129.0 (CH), 128.7 (C_q), 127.8 (CH), 126.0 (CH), 124.8 (C_q), 120.9 (CH), 118.6 (CH), 118.4 (CH), 113.9 (CH), 110.5 (CH), 104.7 (C_q), 60.3 (CH_2), 55.1 (CH_3), 53.8 (CH), 40.7 (CH_2), 37.6 (CH_2), 31.6 (CH_2), 14.0 (CH_3).

IR (ATR): 3397, 3263, 3061, 1751, 1644, 1504, 1248, 1177, 1027, 835, 727, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1049 (10) $[2M+Na]^+$, 536 (100) $[M+Na]^+$.

HR-MS (ESI): *m/z* calcd for $C_{30}H_{32}N_3O_5^+$ 514.2336, found 514.2322 $[M+H]^+$.

Synthesis of Ethyl {2-[2-(2,4-Dimethylphenyl)-1*H*-indol-3-yl]acetyl}-*L*-phenylalanyl-glycinate (100am):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycinate (**99a**) (102 mg, 0.250 mmol) and bis(2,4-dimethylphenyl)-iodonium tosylate (**26m**) (191 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **100am** (50 mg, 39%) as a pale white solid (m. p. = 110–112 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 10.94 (s, 1H), 8.40 (t, *J* = 5.9 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.27–7.20 (m, 7H), 7.14 (s, 1H), 7.04 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 6.92 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 4.59 (ddd, *J* = 9.4, 8.4, 4.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.87 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.82 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.36 (d, *J* = 15.8 Hz, 1H), 3.30 (d, *J* = 15.8 Hz, 1H),3.03 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.79 (dd, *J* = 13.9, 9.4 Hz, 1H), 2.33 (s, 3H), 2.14 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

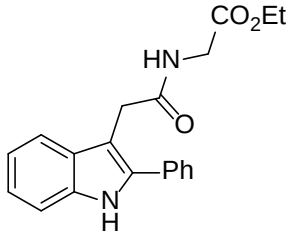
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.5 (C_q), 170.1 (C_q), 169.3 (C_q), 137.5 (C_q), 137.2 (C_q), 136.8 (C_q), 135.9 (C_q), 135.4 (C_q), 130.6 (CH), 130.5 (CH), 129.0 (C_q), 128.9 (CH), 127.8 (CH), 127.6 (C_q), 126.0 (CH), 125.9 (CH), 120.6 (CH), 118.7 (CH), 118.2 (CH), 110.4 (CH), 105.9 (C_q), 60.3 (CH_2), 53.6 (CH), 40.7 (CH_2), 37.6 (CH_2), 31.4 (CH_2), 20.7 (CH_3), 19.7 (CH_3), 14.0 (CH_3).

IR (ATR): 3252, 3058, 1740, 1638, 1194, 739, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 624 (64) $[M-2H+5Na]^+$, 556 (36) $[M-H+2Na]^+$, 510 (100) $[M-H]^+$, 471 (12), 407 (8), 293 (20).

HR-MS (ESI): *m/z* calcd for $C_{31}H_{32}N_3O_4^+$ 510.2387, found 510.2380 $[M–H]^+$.

Synthesis of Ethyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]glycinate (100bh):



The general procedure C was followed using ethyl [2-(1*H*-indol-3-yl)acetyl]glycinate (**99b**) (65 mg, 0.250 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **100bh** (70 mg, 83%) as a pale white solid (m. p. = 114–115 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.86 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.44 (dd, *J* = 8.5, 8.0 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.24 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 7.17 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 6.33 (t, *J* = 6.1 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.92 (d, *J* = 6.1 Hz, 2H), 3.85 (s, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).

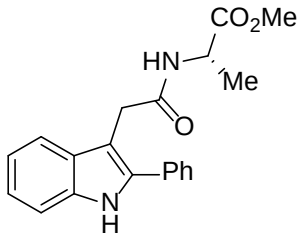
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.7 (C_q), 169.5 (C_q), 136.9 (C_q), 135.9 (C_q), 131.8 (C_q), 129.1 (CH), 128.8 (C_q), 128.3 (CH), 127.9 (CH), 123.0 (CH), 120.5 (CH), 118.9 (CH), 111.1 (CH), 105.1 (C_q), 61.3 (CH_2), 41.4 (CH_2), 32.7 (CH_2), 14.1 (CH_3).

IR (ATR): 3379, 3297, 1720, 1645, 1536, 1451, 1199, 1022, 732 cm^{-1}.

MS (EI) *m/z* (relative intensity) 336 (35) $[M]^+$, 206 (100), 179 (15).

HR-MS (EI): *m/z* calcd for $C_{20}H_{20}N_2O_3^+$ 336.1474, found 336.1467 $[M]^+$.

Synthesis of Methyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]-*L*-alaninate (100ch):



The general procedure C was followed using methyl [2-(1*H*-indol-3-yl)acetyl]-*L*-alaninate (**99c**) (65 mg, 0.250 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **100ch** (69 mg, 82%) as a pale white solid (m. p. = 95–96 °C).

^{1}H NMR(300 MHz, $CDCl_3$): δ = 8.91 (s, 1H), 7.64–7.51 (m, 3H), 7.48–7.33 (m, 4H), 7.23 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 1H), 4.61 (dt, *J* = 7.8, 7.2 Hz, 1H), 3.84 (s, 2H), 3.63 (s, 3H), 1.24 (d, *J* = 7.2 Hz, 3H).

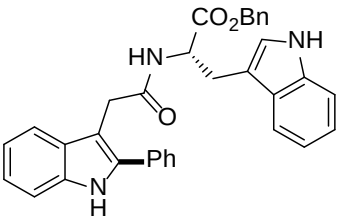
^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C_q), 171.2 (C_q), 136.8 (C_q), 136.0 (C_q), 132.0 (C_q), 129.0 (CH), 128.7 (C_q), 128.1 (CH), 127.8 (CH), 122.7 (CH), 120.2 (CH), 118.6 (CH), 111.2 (CH), 104.8 (C_q), 52.2 (CH_3), 47.9 (CH), 32.8 (CH_2), 17.9 (CH_3).

IR (ATR): 3275, 1737, 1645, 1514, 1450, 1210, 1153, 741, 697 cm^{-1}.

MS (EI) *m/z* (relative intensity) 336 (34) $[M]^+$, 206 (100), 179 (13).

HR-MS (EI): *m/z* calcd for $C_{20}H_{20}N_2O_3^+$ 336.1474, found 336.1479 $[M]^+$.

Synthesis of Benzyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]-*L*-tryptophanate (100dh):



The general procedure C was followed using benzyl [2-(1*H*-indol-3-yl)acetyl]-*L*-tryptophanate (**99d**) (113 mg, 0.250 mmol) and diphenyliodonium tosylate（**26h**）(170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 2/1) yielded **100dh** (103 mg, 78%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ =8.21 (s, 1H), 7.60 (s, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.37–7.28 (m, 9H), 7.42–7.18 (m, 12H), 7.25–7.22 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.11 (ddd, *J*= 8.2, 6.9, 1.0 Hz, 1H), 7.08 (d, *J*= 7.4 Hz, 2H), 7.06 (ddd, *J*=7.9, 6.9, 1.3 Hz, 1H), 6.93 (ddd, *J*=7.9, 6.9, 1.2 Hz, 1H), 6.25 (d, *J*=7.8Hz, 1H), 6.18 (d, *J*=2.0Hz, 1H), 4.99 (d, *J* = 12.2 Hz, 1H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.96 (ddd, *J*=7.8, 6.1, 5.7Hz, 1H), 3.77 (s, 2H), 3.18 (dd, *J* = 14.8, 6.1 Hz, 1H), 3.13 (dd, *J*=14.8, 5.7Hz, 1H).

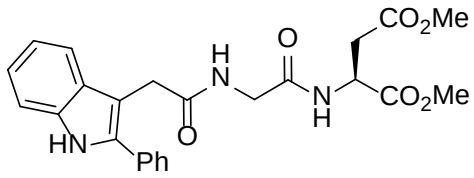
^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3 (C_q), 171.1 (C_q), 136.6 (C_q), 135.8 (C_q), 135.7 (C_q), 135.2 (C_q), 131.6 (C_q), 128.9 (CH), 128.7 (C_q), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.1 (C_q), 122.7 (CH), 122.6 (CH), 121.9 (CH), 120.3 (CH), 119.5 (CH), 118.8 (CH), 118.3 (CH), 110.9 (CH), 110.8 (CH), 109.1 (C_q), 105.1 (C_q), 67.1 (CH_2), 52.5 (CH), 32.9 (CH_2), 27.4 (CH_2).

IR (ATR): 3279, 1732, 1651, 1496, 1455, 1186, 735, 695 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1055 (51) $[2M+H]^+$, 550 (34) $[M+Na]^+$, 528 (100) $[M+H]^+$.

HR-MS (ESI): *m/z* calcd for $C_{34}H_{30}N_3O_3^+$ 528.2282, found 528.2272 $[M+H]^+$.

Synthesis of Dimethyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]glycyl-*L*-aspartate (100eh):



The general procedure C was followed using dimethyl [2-(1*H*-indol-3-yl)acetyl]glycyl-*L*-aspartate (**99e**) (94 mg, 0.250 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/5) yielded **100eh** (77 mg, 68%) as a pale white solid (m. p. = 120–122 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.45 (dd, *J* = 7.6, 7.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.23 (dd, *J* = 8.0, 7.3 Hz, 1H), 7.17 (dd, *J* = 7.8, 7.3 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.49 (t, *J* = 5.4 Hz, 1H), 4.76 (ddd, *J* = 8.7, 4.8, 4.8 Hz, 1H), 3.88 (dd, *J* = 17.0, 5.4 Hz, 1H), 3.85 (s, 2H), 3.81 (dd, *J* = 17.0, 5.4 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.94 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.76 (dd, *J* = 17.1, 4.8 Hz, 1H).

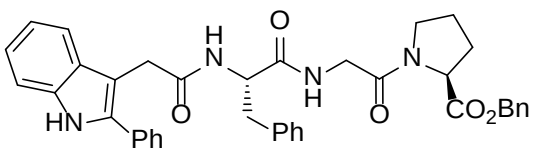
^{13}C NMR(126 MHz, $CDCl_3$): δ = 172.3 (C_q), 171.0 (C_q), 170.7 (C_q), 168.6 (C_q), 136.8 (C_q), 136.0 (C_q), 131.9 (C_q), 128.8 (CH), 128.6 (C_q), 128.0 (CH), 127.9 (CH), 122.5 (CH), 120.1 (CH), 118.4 (CH), 111.2 (CH), 104.5 (C_q), 52.6 (CH_3), 51.9 (CH_3), 48.3 (CH), 43.0 (CH_2), 35.8 (CH_2), 32.6 (CH_2).

IR (ATR): 3276, 2875, 1735, 1642, 1528, 1335, 745 cm^{-1}.

MS (EI) *m/z* (relative intensity) 451 (9) $[M]^+$, 291 (6), 233 (61), 206 (100), 179 (11).

HR-MS (EI): *m/z* calcd for $C_{24}H_{25}N_3O_6^+$ 451.1743, found 451.1731 $[M]^+$.

Synthesis of Benzyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycyl-*L*-prolinate (100fh):



The general procedure C was followed using benzyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycyl-*L*-prolinate (**99f**) (142 mg, 0.250 mmol) and diphenyliodonium tosylate (**26h**) (170 mg, 0.375 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc: 1/1) yielded **100fh** (127 mg,

79%) as a pale white solid (m. p. = 102–103 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.45–7.37 (m, 4H), 7.37–7.29 (m, 4H), 7.22 (dd, *J* = 8.2, 1.3, 0.9 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.10–7.03 (m, 2H), 6.85 (t, *J* = 8.7 Hz, 1H), 6.84 (t, *J* = 4.7 Hz, 1H),6.72 (d, *J* = 8.3 Hz, 2H), 6.23 (d, *J* = 8.8 Hz, 1H), 5.17 (dd, *J* = 12.7, 6.7 Hz, 2H), 4.74 (ddd, *J* = 8.8, 7.4, 5.6 Hz, 1H), 4.56 (dd, *J* = 8.3, 3.1 Hz, 1H), 3.96 (dd, *J* = 17.5, 4.7 Hz, 1H), 3.85 (dd, *J* = 17.5, 4.7 Hz, 1H), 3.79 (d, *J* = 8.7 Hz, 2H), 3.53 (dd, *J* = 13.6, 6.7 Hz, 1H), 3.40 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.97 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.86 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.25–2.13 (m, 1H), 2.06–1.93 (m, 3H).

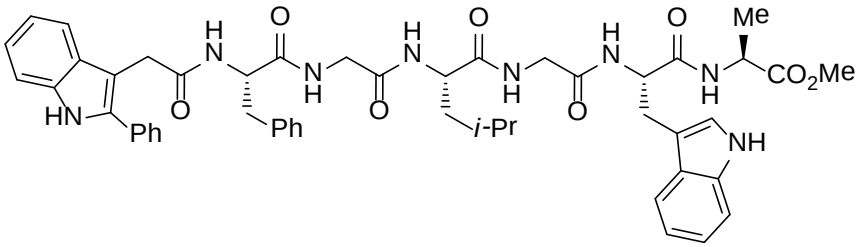
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 (C_q),171.6 (C_q), 170.5 (C_q), 166.4 (C_q), 136.6 (C_q), 136.0 (C_q), 135.8 (C_q), 135.5 (C_q), 131.8 (C_q), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (C_q), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 126.7 (CH), 122.9 (CH), 120.6 (CH), 118.8 (CH), 111.0 (CH), 105.0 (C_q), 67.0 (CH_2), 59.0 (CH), 54.1 (CH), 45.9 (CH_2), 41.9 (CH_2), 37.6 (CH_2), 32.8 (CH_2), 29.0 (CH_2), 24.6 (CH_2).

IR (ATR): 3284, 1740, 1634, 1496, 1452, 1168, 741, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity) 642 (8) $[M]^+$, 380 (11), 233 (74), 206 (100), 179 (14).

HR-MS (EI): *m/z* calcd for $C_{39}H_{38}N_4O_5^+$ 642.2842, found 642.2841 $[M]^+$.

Synthesis of Methyl [2-(2-Phenyl-1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycyl-*L*-leucyl-glycyl-*L*-tryptophyl-*L*-alaninate (100gh):



The general procedure C was followed using methyl [2-(1*H*-indol-3-yl)acetyl]-*L*-phenylalanyl-glycyl-*L*-leucyl-glycyl-*L*-tryptophyl-*L*-alaninate (**99g**) (82 mg, 0.1 mmol) and diphenyliodonium tosylate (**26h**) (68 mg, 0.15 mmol) in DMF (2 mL). After 17 h, purification by column chromatography (EtOAc/MeOH: 50/1) yielded **100gh** (78 mg, 87%) as a pale white solid (m. p. = 169–171 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.16 (s, 1H), 10.76 (s, 1H), 8.38 (d, *J* = 7.1 Hz, 1H), 8.24 (t, *J* = 5.7 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 8.09 (t, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.37–7.34 (m, 1H), 7.33–7.28 (m, 3H), 7.25–7.16 (m, 5H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.07 (ddd, *J*= 7.9, 6.9, 1.3 Hz, 1H), 7.03 (ddd, *J*= 7.9, 6.9, 1.3 Hz, 1H), 6.97 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 6.91 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 4.65–4.55 (m, 2H), 4.35–4.25 (m, 2H), 3.77 (d, *J* = 5.4 Hz, 2H), 3.67 (dd, *J* = 15.5, 6.3 Hz, 1H), 3.60 (s, 3H), 3.58–3.55 (m, 3H), 3.14 (dd, *J* = 14.7, 4.7 Hz, 1H), 3.07 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.92 (dd, *J* = 14.7, 8.6 Hz, 1H), 2.84 (dd, *J* = 13.8, 9.6 Hz, 1H), 1.60 (qqt, *J* = 6.6, 6.6, 5.6 Hz, 1H), 1.46 (dd, *J* = 10.5, 5.6 Hz, 2H), 1.28 (d, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 172.5 (C_q), 171.9 (C_q), 171.4 (C_q), 171.0 (C_q), 170.6 (C_q), 168.3 (C_q), 168.1 (C_q), 137.6 (C_q), 135.8 (C_q), 135.7 (C_q), 135.6 (C_q), 132.2 (C_q), 128.9 (CH), 128.6 (C_q), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 127.1 (C_q), 126.0 (CH), 123.4 (CH), 121.2 (CH), 120.6 (CH), 118.8 (CH), 118.5 (CH), 118.2 (CH), 118.0 (CH), 111.0 (CH), 110.7 (CH), 109.7 (C_q), 105.5 (C_q), 54.2 (CH), 53.0 (CH), 51.7 (CH_3), 51.0 (CH), 47.5 (CH), 41.9 (CH_2), 41.8 (CH_2), 40.8 (CH_2), 37.5 (CH_2), 31.6 (CH_2), 27.7 (CH_2), 24.0 (CH), 22.9 (CH_3), 21.5 (CH_3), 16.8 (CH_3).

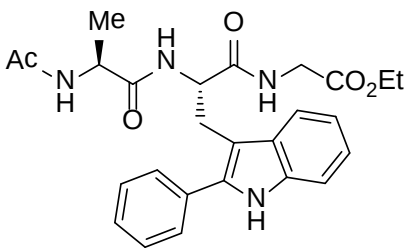
IR (ATR): 3289, 1744, 1623, 1518, 1216, 739, 697 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 931 (56) $[M+2NH_4–H]^+$, 895 (100) $[M–H]^+$, 855 (28), 819 (46) $[M–Ph]^+$.

HR-MS (ESI): *m/z* calcd for $C_{50}H_{56}N_8NaO_8^+$ 919.4113, found 919.4122 $[M+Na]^+$.

5.4.5 Analytical Data for Arylated Tryptophan-Containing Peptides

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-phenyltryptophyl-glycinate (102ah):



The general procedure D1 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and diphenyliodonium tosylate (**26h**) (136 mg, 0.3 mmol). After 17 h, purification by column chromatography (DCM/MeOH: 15/1) yielded **102ah** (95 mg, 99%) as a pale white solid (m. p. = 212–214 °C).

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and diphenyliodonium tosylate (**26h**) (136 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (DCM/MeOH: 15/1) yielded **102ah** (67 mg, 70%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.16 (s, 1H), 8.15 (t, *J* = 5.8 Hz, 1H), 7.96 (d, *J* = 7.1 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.66 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.36 (dddd, *J* = 7.6, 7.6, 1.1, 1.1 Hz, 1H), 7.31 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.0, 1.2 Hz,1H), 6.99 (ddd, *J* = 7.8, 7.0, 1.3 Hz, 1H), 4.65 (ddd, *J* = 8.3, 7.2, 7.2 Hz, 1H), 4.19 (dq, *J* = 7.1, 7.1 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.67 (dd, *J* = 17.5, 5.8 Hz, 1H), 3.56 (dd, *J* = 17.5, 5.8 Hz, 1H), 3.29 (dd, *J* = 15.3, 7.2 Hz, 1H), 3.08 (dd, *J* = 15.3, 7.2 Hz, 1H), 1.77 (s, 3H), 1.12 (t, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H).

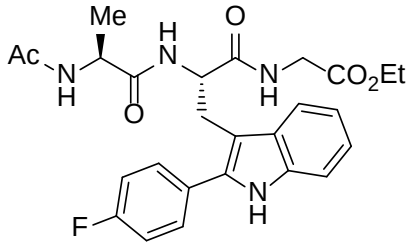
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.7 (C_q), 171.3 (C_q), 169.0 (C_q), 169.0 (C_q), 135.7 (C_q), 135.2 (C_q), 132.5 (C_q), 128.8 (C_q), 128.3 (CH), 128.0 (CH), 127.1 (CH), 121.2 (CH), 119.0 (CH), 118.4 (CH), 110.8 (CH), 107.3 (C_q), 60.2 (CH_2), 53.7 (CH), 48.3 (CH), 40.8 (CH_2), 27.9 (CH_2), 22.4 (CH_3), 17.7 (CH_3), 14.0 (CH_3).

IR (ATR): 3273, 1752, 1632, 1541, 1376, 1203, 1023, 748, 699 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 979 (25) $[2M+Na]^+$, 501 (100) $[M+Na]^+$, 479 (75) $[M+H]^+$, 366 (12), 235 (13).

HR-MS (ESI): *m/z* calcd for $C_{26}H_{31}N_4O_5^+$ 479.2289, found 479.2294 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(4-fluorophenyl)tryptophyl-glycinate (102ai):



The general procedure D1 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-fluorophenyl)iodonium tosylate (**26i**) (147 mg, 0.3 mmol). After 17 h, purification by column chromatography (DCM/MeOH: 15/1) yielded (**102ai**) (92 mg, 93%) as a pale white solid (m. p. = 208–210 °C).

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-fluorophenyl)iodonium tosylate (**26i**) (147 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (DCM/MeOH: 15/1)

yielded **102ai** (94 mg, 95%) as a pale white solid.

^{1}H NMR(500 MHz, d_6-DMSO): δ = 11.13 (s, 1H), 8.11 (t, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.73–7.68 (m, 2H), 7.66 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.34–7.27 (m, 3H), 7.09 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.98 (ddd, *J* = 7.9, 7.0, 1.3 Hz, 1H), 4.64 (ddd, *J* = 8.4, 7.1, 7.1 Hz, 1H), 4.19 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.03 (dq, *J* = 7.1, 1,7 Hz, 2H), 3.70 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.59 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.25 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.06 (dd, *J* = 14.4, 7.1 Hz, 1H), 1.79 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.7 (C_q), 171.2 (C_q), 169.0 (C_q), 169.0 (C_q), 162.2 (d, $J_{C\text{-}F}$ = 244.4 Hz, C_q), 135.6 (C_q), 134.3 (C_q), 130.1 (d, $J_{C\text{-}F}$ = 8.1 Hz, CH), 129.1 (d, $J_{C\text{-}F}$ = 3.0 Hz, C_q), 128.6 (C_q), 121.2 (CH), 118.9 (CH), 118.5 (CH), 115.2 (d, $J_{C\text{-}F}$ = 21.3 Hz, CH), 110.8 (CH), 107.3 (C_q), 60.2 (CH_2), 53.6 (CH), 48.2 (CH), 40.8 (CH_2), 27.8 (CH_2), 22.4 (CH_3), 17.7 (CH_3), 13.9 (CH_3).

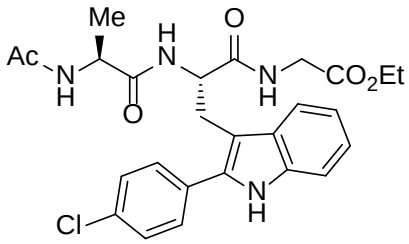
^{19}F NMR (282 MHz, d_6-DMSO): δ = –110.03 (dd, *J* = 9.9, 4.4 Hz).

IR (ATR): 3272, 1748, 1632, 1539, 1213, 1163, 845, 747 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1015 (33) $[2M+Na]^+$, 519 (100) $[M+Na]^+$, 497 (74) $[M+H]^+$, 384 (12), 253 (15).

HR-MS (ESI): *m/z* calcd for $C_{26}H_{30}FN_4O_5^+$ 497.2195, found 497.2200 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(4-chlorophenyl)tryptophyl-glycinate (102aj):



The general procedure D1 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-chlorophenyl)iodonium tosylate (**26j**) (156 mg, 0.3 mmol). After 17 h, purification by column chromatography (DCM/MeOH: 15/1) yielded **102aj** (96 mg, 94%) as a pale white solid (m. p. = 241–243 °C).

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-chlorophenyl)iodonium tosylate (**26j**) (156 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (DCM/MeOH: 15/1) yielded **102aj** (66 mg, 64%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.19 (s, 1H), 8.15 (t, *J* = 5.8 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 8.0, 7.5 Hz, 1H), 6.99 (dd, *J* = 7.9, 7.5 Hz, 1H), 4.65 (ddd, *J* = 8.4, 7.1, 7.1 Hz, 1H), 4.19 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.03 (dq, *J* = 7.1, 1,7 Hz, 2H), 3.70 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.59 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.25 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.08 (dd, *J* = 14.4, 7.1 Hz, 1H), 1.80 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H).

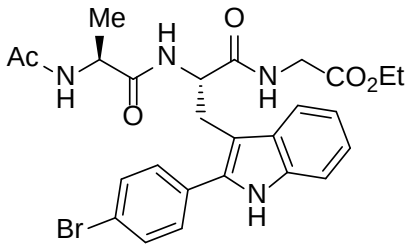
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.8 (C_q), 171.2 (C_q), 169.0 (C_q), 169.0 (C_q), 135.8 (C_q), 133.9 (C_q), 131.8 (C_q), 131.4 (C_q), 129.7 (CH), 128.7 (C_q), 128.3 (CH), 121.5 (CH), 119.1 (CH), 118.6 (CH), 110.9 (CH), 107.9 (C_q), 60.3 (CH_2), 53.6 (CH), 48.3 (CH), 40.8 (CH_2), 27.9 (CH_2), 22.4 (CH_3), 17.7 (CH_3), 14.0 (CH_3).

IR (ATR): 3273, 1750, 1631, 1534, 1201, 1092, 748, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1051/1049/1047/ (3/19/29) $[2M+Na]^+$, 537/535 (32/100) $[M+Na]^+$, 515/513 (20/61) $[M+H]^+$, 402/400 (4/11), 271/269 (5/14).

HR-MS (ESI): m/z calcd for $C_{26}H_{30}ClN_4O_5^+$ 513.1899, found 513.1905 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(4-bromophenyl)tryptophyl-glycinate (118ak):



The general procedure D1 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-bromophenyl)iodonium tosylate (**26k**) (183 mg, 0.3 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102ak** (88 mg, 79%) as a pale white solid (m. p. = 239–241 °C).

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-bromophenyl)iodonium tosylate (**26k**) (183 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102ak** (60 mg, 54%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.19 (s, 1H), 8.14 (t, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.69–7.62 (m, 5H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.10 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.00 (ddd, *J* = 7.9, 7.0 Hz, 1H), 4.65 (ddd, *J* = 8.3, 7.1, 7.1 Hz, 1H), 4.20

(dq, *J* = 7.2, 7.2 Hz, 1H), 4.04 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.70 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.59 (dd, *J* = 17.7, 5.8 Hz, 1H), 3.28 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.08 (dd, *J* = 14.4, 7.1 Hz, 1H), 1.79 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H).

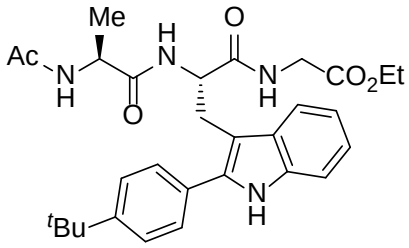
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.7 (C_q), 171.2 (C_q), 169.0 (C_q), 169.0 (C_q), 135.8 (C_q), 133.9 (C_q), 131.7 (C_q), 131.2 (CH), 129.9 (CH), 128.7 (C_q), 121.5 (CH), 120.3 (C_q), 119.0 (CH), 118.6 (CH), 110.9 (CH), 107.9 (C_q), 60.3 (CH_2), 53.6 (CH), 48.3 (CH), 40.8 (CH_2), 27.9 (CH_2), 22.4 (CH_3), 17.7 (CH_3), 13.9 (CH_3).

IR (ATR): 3273, 1737, 1631, 1538, 1192, 827, 738, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1139/1137/1135 (15/30/15) $[2M+Na]^+$, 581/579 (100/100) $[M+Na]^+$, 559/557 (63/63) $[M+H]^+$, 446/444 (14/14), 315/313 (13/13).

HR-MS (ESI): *m/z* calcd for $C_{26}H_{30}BrN_4O_5^+$ 557.1394, found 557.1400 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(4-*tert*-butylphenyl)tryptophyl-glycinate (102al):



The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-*tert*-butylphenyl)iodonium tosylate (**26l**) (169 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/ MeOH: 1/4/0.2) yielded **102al** (82 mg, 77%) as a pale white solid (m. p. = 168–170 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.05 (s, 1H), 8.12 (t, *J* = 5.8 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.31 (dd, *J* = 8.1 Hz, 1H), 7.06 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.97 (dd, *J* = 8.0, 7.2 Hz, 1H), 4.65 (ddd, *J* = 8.2, 7.1, 7.1 Hz, 1H), 4.19 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.03 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.69 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.57 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.32 (dd, *J* = 14.5, 7.1 Hz, 1H), 3.11 (dd, *J* = 14.5, 7.1 Hz, 1H), 1.78 (s, 3H), 1.34 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.7 (C_q), 171.3 (C_q), 169.1 (C_q), 169.0 (C_q), 149.4 (C_q), 135.6 (C_q), 135.1 (C_q), 129.7 (C_q), 128.8 (CH), 127.6 (CH), 125.1 (CH), 121.0 (CH), 118.9 (CH), 118.3 (CH), 110.7 (C_q), 107.0 (C_q), 60.2 (CH_2), 53.7 (CH), 48.3 (CH), 40.8

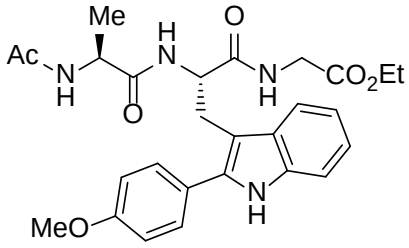
(CH_2), 34.3 (CH_2), 31.0 (CH_3), 27.9 (C_q), 22.4 (CH_3), 17.7 (CH_3), 13.9 (CH_3).

IR (ATR): 3280, 2962, 1738, 1639, 1507, 1196, 1019, 836, 741 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1091 (50) $[2M+Na]^+$, 557 (100) $[M+Na]^+$, 535 (92) $[M+H]^+$, 422 (8), 291 (4).

HR-MS (ESI): *m/z* calcd for $C_{30}H_{39}N_4O_5^+$ 535.2915, found 535.2920 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(4-methoxyphenyl)tryptophyl-glycinate (102ag):



The general procedure D1 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-methoxyphenyl)iodonium tosylate (**26g**) (154 mg, 0.3 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102ag** (86 mg, 85%) as a pale white solid (m. p. = 230–232 °C).

The general procedure D2 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and (mesityl)(4-methoxyphenyl)iodonium tosylate (**26r**) (157 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102ag** (65 mg, 64%) as a pale white solid.

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(4-methoxyphenyl)iodonium tosylate (**26g**) (154 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102ag** (81 mg, 80%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.03 (s, 1H), 8.09 (t, *J* = 5.7 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* =8.0, 7.0 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 8.2, 7.0 Hz, 1H), 4.64 (ddd, *J* = 8.3, 7.0, 7.0 Hz, 1H), 4.20 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.04 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.82 (s, 3H), 3.71 (dd, *J* = 17.3, 5.7 Hz, 1H), 3.60 (dd, *J* = 17.3, 5.7 Hz, 1H), 3.27 (dd, *J* = 14.4, 7.0 Hz, 1H), 3.06 (dd, *J* = 14.4, 7.0 Hz, 1H), 1.79 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.6 (C_q), 171.3 (C_q), 169.0 (C_q), 169.0 (C_q), 158.4 (C_q), 135.5 (C_q), 135.2 (C_q), 129.2 (CH), 128.8 (C_q), 125.0 (C_q), 120.8 (CH), 118.7 (CH),

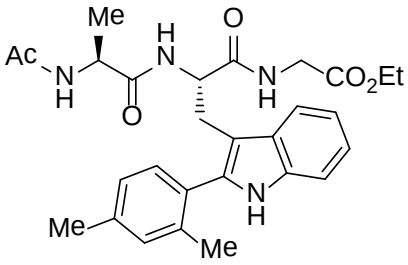
118.3 (CH), 113.8 (CH), 110.6 (CH), 106.4 (C_q), 60.2 (CH_2), 55.1 (CH_3), 53.67 (CH), 48.3 (CH), 40.8 (CH_2), 27.9 (CH_2), 22.4 (CH_3), 17.7 (CH_3), 14.0 (CH_3).

IR (ATR): 3279, 1733, 1632, 1539, 1246, 1181, 1033, 775, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1039 (63) $[2M+Na]^+$, 531 (94) $[M+Na]^+$, 509 (100) $[M+H]^+$, 396 (9), 265 (13).

HR-MS (ESI): *m/z* calcd for $C_{27}H_{33}N_4O_6^+$ 509.2395, found 509.2400 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(2,4-dimethylphenyl)tryptophyl-glycinate (102am):



The general procedure D1 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(2,4-dimethylphenyl)iodonium tosylate (**26m**) (153 mg, 0.3 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102am** (52 mg, 51%) as a pale white solid (m. p. = 144–146 °C).

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(2,4-dimethylphenyl)iodonium tosylate (**26m**) (153 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102am** (72 mg, 71%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 10.87 (s, 1H), 7.97 (t, *J* = 5.7 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 8.2, 7.5 Hz, 1H), 6.99 (dd, *J* = 7.8, 7.5 Hz, 1H), 4.52 (ddd, *J* = 8.3, 7.8, 7.8 Hz, 1H), 4.16 (dq, *J* = 7.3, 7.3 Hz, 1H), 4.04 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.69 (dd, *J* = 17.4, 5.7 Hz, 1H), 3.62 (dd, *J* = 17.4, 5.7 Hz, 1H), 3.06 (dd, *J* = 14.3, 7.8 Hz, 1H), 2.82 (dd, *J* = 14.3, 7.8 Hz, 1H), 2.35 (s, 3H), 2.12 (s, 3H), 1.77 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.5 (C_q), 171.3 (C_q), 169.1 (C_q), 168.8 (C_q), 137.1 (C_q), 136.8 (C_q), 135.8 (C_q), 135.5 (C_q), 130.7 (CH), 130.4 (CH), 129.4 (C_q), 127.8 (C_q), 125.9 (CH), 120.5 (CH), 118.6 (CH), 118.1 (CH), 110.58 (CH), 107.2 (C_q), 60.2 (CH_2), 53.5 (CH), 48.2 (CH), 40.7 (CH_2), 27.5 (CH_2), 22.4 (CH_3), 20.8 (CH_3), 19.6 (CH_3), 17.8 (CH_3),

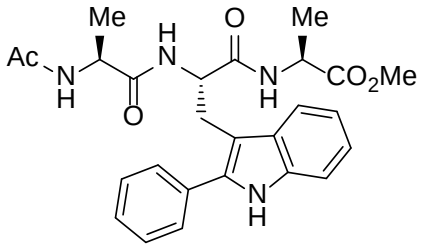
13.9 (CH_3).

IR (ATR): 3279, 2982, 1626, 1523, 1458, 1371, 1194, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1035 (59) $[2M+Na]^+$, 529 (91) $[M+Na]^+$, 507 (100) $[M+H]^+$, 394 (13), 263 (14).

HR-MS (ESI): *m/z* calcd for $C_{28}H_{35}N_4O_5^+$ 507.2602, found 507.2607 $[M+H]^+$.

Synthesis of Methyl Acetyl-*L*-alanyl-*L*-phenyltryptophyl-*L*-alaninate (102bh):



The general procedure D1 was followed using methyl acetyl-*L*-alanyl-*L*-tryptophyl-*L*-alaninate (**101b**) (80 mg, 0.2 mmol) and diphenyliodonium tosylate (**26h**) (136 mg, 0.3 mmol). After 17 h, purification by column chromatography (DCM/MeOH: 15/1) yielded **102bh** (94 mg, 98%) as a pale white solid (m. p. = 253–255 °C).

The general procedure D3 was followed using methyl acetyl-*L*-alanyl-*L*-tryptophyl-*L*-alaninate (**101b**) (80 mg, 0.2 mmol) and diphenyliodonium tosylate (**26h**) (136 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102bh** (52 mg, 54%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.12 (s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.48 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.37 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.98 (dd, *J* = 7.5, 7.0 Hz, 1H), 4.61 (ddd, *J* = 8.3, 7.6, 7.6 Hz, 1H), 4.20 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.11 (dq, *J* = 7.2, 7.2 Hz, 1H), 3.49 (s, 3H), 3.34 (dd, *J* = 14.6, 7.6 Hz, 1H), 3.11 (dd, *J* = 14.6, 7.6 Hz, 1H), 1.80 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 172.2 (C_q), 171.6 (C_q), 170.6 (C_q), 169.2 (C_q), 135.7 (C_q), 135.1 (C_q), 132.6 (C_q), 128.8 (C_q), 128.3 (CH), 127.9 (CH), 127.0 (CH), 121.2 (CH), 119.0 (CH), 118.4 (CH), 110.8 (CH), 107.4 (C_q), 53.7 (CH_3), 51.6 (CH), 48.6 (CH), 47.5 (CH), 27.4 (CH_2), 22.4 (CH_3), 17.4 (CH_3), 16.9 (CH_3).

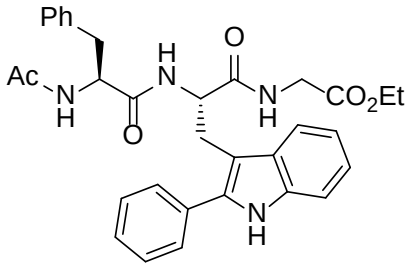
IR (ATR): 3273, 1743, 1633, 1538, 1201, 1055, 742, 696 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 979 (24) $[2M+Na]^+$, 501 (100) $[M+Na]^+$, 479 (56) $[M+H]^+$,

366 (8), 235 (13).

HR-MS (ESI): *m/z* calcd for $C_{26}H_{31}N_4O_5^+$ 479.2289, found 479.2294 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-phenylalanyl-*L*-phenyltryptophyl-glycinate (102ch):



The general procedure D1 was followed using ethyl acetyl-*L*-phenylalanyl-*L*-tryptophyl-glycinate (**101c**) (122 mg, 0.255 mmol) and diphenyliodonium tosylate (**26h**) (173 mg, 0.382 mmol). After 17 h, purification by column chromatography (DCM/MeOH: 10/1) yielded **102ch** (122 mg, 86%) as a pale white solid (m. p. = 215–217 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.18 (s, 1H), 8.24 (t, *J* = 5.6 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 2H), 7.47 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.37 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 7.16–7.12 (m, 3H), 7.08 (dd, *J* = 8.1, 7.0 Hz, 1H), 6.98 (dd, *J* = 7.9, 7.0 Hz, 1H), 4.69 (ddd, *J* = 8.2, 7.2, 7.2 Hz, 1H), 4.46 (ddd, *J* = 9.8, 8.3, 4.5 Hz, 1H), 4.01 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.68 (dd, *J* = 17.3, 5.6 Hz, 1H), 3.55 (dd, *J* = 17.3, 5.6 Hz, 1H), 3.28 (dd, *J* = 14.5, 7.2 Hz, 1H), 3.07 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.87 (dd, *J* = 13.9, 4.5 Hz, 1H), 2.64 (dd, *J* = 13.9, 9.8 Hz, 1H), 1.68 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H).

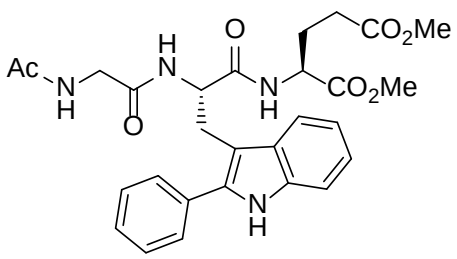
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.2 (C_q), 170.6 (C_q), 169.0 (C_q), 168.8 (C_q), 137.7 (C_q), 135.7 (C_q), 135.3 (C_q), 132.5 (C_q), 128.9 (CH), 128.7 (C_q), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 125.9 (CH), 121.2 (CH), 119.0 (CH), 118.4 (CH), 110.8 (CH), 107.1 (C_q), 60.2 (CH_2), 53.8 (CH), 53.7 (CH), 40.8 (CH_2), 37.2 (CH_2), 28.2 (CH_2), 22.4 (CH_3), 14.0 (CH_3).

IR (ATR): 3444, 1661, 1051, 1023, 1004, 821, 759 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1131 (16) $[2M+Na]^+$, 577 (100) $[M+Na]^+$, 555 (32) $[M+H]^+$, 430 (6), 366 (8).

HR-MS (ESI): *m/z* calcd for $C_{32}H_{34}N_4NaO_5^+$ 557.2421, found 557.2427 $[M+Na]^+$.

Synthesis of Dimethyl Acetyl-glycyl-*L*-phenyltryptophyl-*L*-glutamate (102dh):



The general procedure D1 was followed using dimethyl acetyl-glycyl-*L*-tryptophyl-*L*-glutamate

(**101d**) (92 mg, 0.2 mmol) and diphenyliodonium tosylate (**26h**) (136 mg, 0.3 mmol). After 17 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102dh** (60 mg, 56%) as a pale white solid (m. p. = 172–174 °C).

The general procedure D3 was followed using dimethyl acetyl-glycyl-*L*-tryptophyl-*L*-glutamate (**101d**) (92 mg, 0.2 mmol) and diphenyliodonium tosylate (**26h**) (136 mg, 0.3 mmol) with water (3.0 mL). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102dh** (25 mg, 23%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.12 (s, 1H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.98 (t, *J* = 5.5 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.48 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.37 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.1 Hz, 1H), 6.98 (dd, *J* = 7.9, 7.1 Hz, 1H), 4.68 (ddd, *J* = 8.4, 7.8, 7.8 Hz, 1H), 4.24 (dt, *J* = 7.7, 5.5 Hz, 1H), 3.64 (dd, *J* = 16.5, 5.7 Hz, 1H), 3.57 (s, 3H), 3.48 (s, 3H), 3.45 (dd, *J* = 16.5, 5.7 Hz, 1H), 3.31 (d, *J* = 14.4, 7.8 Hz, 1H), 3.07 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.28 (t, *J* = 7.7 Hz, 2H), 1.94 (dt, *J* = 7.7, 5.5 Hz, 1H), 1.82 (dt, *J* = 7.7, 5.5 Hz, 1H), 1.80 (s, 3H).

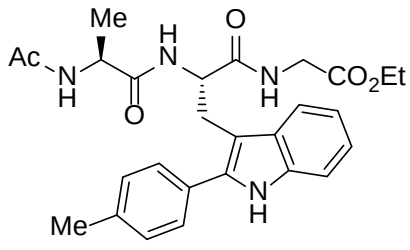
^{13}C NMR (126 MHz, d_6-DMSO): δ = 172.3 (C_q), 171.2 (C_q), 171.0 (C_q), 169.4 (C_q), 168.3 (C_q), 135.7 (C_q), 135.1 (C_q), 132.5 (C_q), 128.7 (C_q), 128.3 (CH), 127.9 (CH), 127.0 (CH), 121.1 (CH), 118.9 (CH), 118.4 (CH), 110.8 (CH), 107.3 (C_q), 53.7 (CH), 51.6 (CH), 51.2 (CH_3), 51.0 (CH_3), 42.1 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 26.0 (CH_2), 22.3 (CH_3).

IR (ATR): 3272, 1733, 1635, 1521, 1436, 1204, 742, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1095 (29) $[2M+Na]^+$, 559 (100) $[M+Na]^+$, 537 (67) $[M+H]^+$, 438 (4), 362 (4).

HR-MS (ESI): *m/z* calcd for $C_{28}H_{33}N_4O_7^+$ 537.2344, found 537.2349 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(4-tolyl)tryptophyl-glycinate (102as):



The general procedure D2 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and (mesityl)(*p*-tolyl)iodonium tosylate (**26s**) (152 mg, 0.3 mmol) with water. After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102as** (54 mg, 55%) as a pale white solid (m. p. = 210–212 °C).

The general procedure D3 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and bis(*p*-tolyl)iodonium tosylate (**26x**) (144 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.2) yielded **102as** (60 mg, 61%) as a pale white solid.

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.05 (s, 1H), 8.08 (t, *J* = 5.7 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 2H), 7.06 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.97 (dd, *J* = 7.9, 7.0 Hz, 1H), 4.64 (ddd, *J* = 8.3, 7.1, 7.1 Hz, 1H), 4.18 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.04 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.70 (dd, *J* = 17.2, 5.7 Hz, 1H), 3.58 (dd, *J* = 17.2, 5.7 Hz, 1H), 3.28 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.09 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.37 (s, 3H), 1.79 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H).

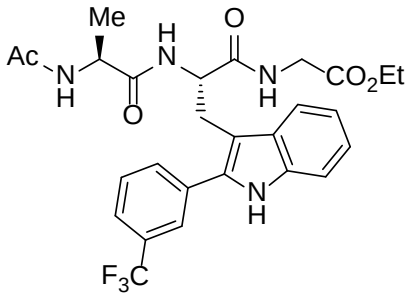
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.6 (C_q), 171.3 (C_q), 169.1 (C_q),169.0 (C_q), 136.4 (C_q), 135.6 (C_q), 135.3 (C_q), 129.7 (C_q), 128.9 (CH), 128.8 (C_q), 127.8 (CH), 121.0 (CH), 118.8 (CH), 118.3 (CH), 110.7 (CH), 106.9 (C_q), 60.2 (CH_2), 53.70 (CH), 48.3 (CH), 40.8 (CH_2), 27.9 (CH_2), 22.4 (CH_3), 20.8 (CH_3), 17.7 (CH_3), 13.9 (CH_3).

IR (ATR): 3272, 1733, 1632, 1540, 1193, 1025, 742 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1007 (44) $[2M+Na]^+$, 515 (100) $[M+Na]^+$, 493 (89) $[M+H]^+$, 380 (14), 249 (11).

HR-MS (ESI): m/z calcd for $C_{27}H_{33}N_4O_5^+$ 443.2445, found 493.2451 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(3-trifluoromethylphenyl)tryptophyl-glycinate (102at):



The general procedure D2 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and (mesityl)(3-trifluoromethylphenyl)-iodonium tosylate (**26t**) (169 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/1) yielded **102at** (36 mg, 33%) as a pale white solid (m. p. = 192–194 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.30 (s, 1H), 8.10 (t, *J* = 5.8 Hz, 1H), 8.03–8.00 (m,

1H), 7.94 (s, 1H), 7.92–7.88 (m, 2H), 7.73–7.68 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.12 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.01 (dd, *J* = 7.9, 7.5 Hz, 1H), 4.65 (ddd, *J* = 8.4, 7.3, 7.3 Hz, 1H), 4.19 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.02 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.65 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.56 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.34 (dd, *J* = 14.4, 7.3 Hz, 1H), 3.12 (dd, *J* = 14.4, 7.3 Hz, 1H), 1.79 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.7 (C_q), 171.0 (C_q), 169.0 (C_q), 168.9 (C_q), 135.9 (C_q), 133.5 (C_q), 133.4 (C_q), 131.9 (CH), 129.4 (CH), 129.2 (q, J_{C-F} = 31.6 Hz, C_q), 128.6 (C_q), 124.2 (q, J_{C-F} = 3.8 Hz, CH), 124.0 (q, J_{C-F} = 271.7 Hz, CF_3), 123.5 (q, J_{C-F} = 3.8 Hz, CH), 121.8 (CH), 119.2 (CH), 118.7 (CH), 111.0 (CH), 108.4 (C_q), 60.2 (CH_2), 53.4 (CH), 48.2 (CH), 40.7 (CH_2), 27.8 (CH_2), 22.4 (CH_3), 17.7 (CH_3), 13.9 (CH_3).

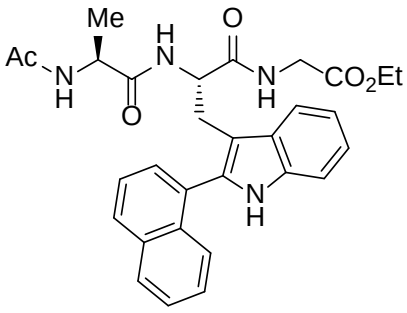
^{19}F NMR (376 MHz, d_6-DMSO): δ = –61.02 (s).

IR (ATR): 3266, 1719, 1635, 1542, 1327, 1024, 1000, 690 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1115 (56) $[2M+Na]^+$, 569 (100) $[M+Na]^+$, 547 (100) $[M+H]^+$, 434 (19), 303 (16).

HR-MS (ESI): *m/z* calcd for $C_{27}H_{30}F_3N_4O_5^+$ 547.2163, found 547.2168 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(naphthalen-1-yl)tryptophyl-glycinate (102au):



The general procedure D2 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and (mesityl)(naphthalen-1-yl)iodonium tosylate (**26u**) (163 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/1) yielded **102au** (74 mg, 70%) as a pale white solid (m. p. = 128–130 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.18 (s, 1H), 8.03 (d, *J* = 7.0 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 5.3 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.66–7.60 (m, 3H), 7.57–7.52 (m, 2H), 7.47 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.34 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.06 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 4.55 (ddd, *J* = 8.3, 7.3, 7.3 Hz, 1H), 4.12 (dq, *J* = 7.0, 7.0 Hz, 1H), 4.00 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.53 (dd, *J* = 17.2, 5.3 Hz, 1H), 3.47 (dd, *J* = 17.2, 5.3 Hz, 1H), 3.09 (d, *J* = 14.4 Hz, 1H),

2.86 (d, *J* = 14.4 Hz, 1H), 1.77 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H).

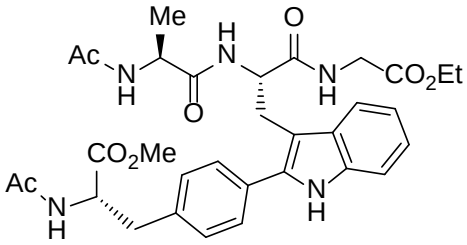
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.5 (C_q), 171.1 (C_q), 169.0 (C_q), 168.8 (C_q), 135.8 (C_q), 134.3 (C_q), 133.0 (C_q), 131.9 (C_q), 130.2 (C_q), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.8 (C_q), 126.2 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 120.9 (CH), 118.8 (CH), 118.4 (CH), 110.8 (CH), 108.7 (C_q), 60.2 (CH_2), 53.5 (CH), 48.2 (CH), 40.6 (CH_2), 27.8 (CH_2), 22.4 (CH_3), 17.8 (CH_3), 13.9 (CH_3).

IR (ATR): 3281, 1736, 1636, 1506, 1371, 1197, 779, 743 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1079 (58) $[2M+Na]^+$, 551 (96) $[M+Na]^+$, 529 (100) $[M+H]^+$, 416 (17), 285 (13).

HR-MS (ESI): m/z calcd for $C_{30}H_{33}N_4O_5^+$ 529.2445, found 529.2451 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(*N*-acetyl-*L*-phenylalanine)tryptophyl-glycinate (102av):



The general procedure D2 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and (mesityl)(*N*-acetyl-*L*-phenylalanine)iodonium tosylate (**26v**) (191 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.4) yielded **102av** (66 mg, 53%) as a pale white solid (m. p. = 176–178 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.10 (s, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.10 (t, *J* = 5.7 Hz, 1H), 7.91 (d, *J* = 7.1 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.97 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 4.65 (ddd, *J* = 8.3, 7.1, 7.1 Hz, 1H), 4.52 (ddd, *J* = 9.3, 7.7, 5.7 Hz, 1H), 4.19 (dq, *J* = 7.1, 7.1 Hz, 1H), 4.02 (dq, *J* = 7.2, 1.7 Hz, 2H), 3.70 (dd, *J* = 17.3, 5.7 Hz, 1H), 3.63 (s, 3H), 3.58 (dd, *J* = 17.3, 5.7 Hz, 1H), 3.29 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.10 (dd, *J* = 14.4, 7.1 Hz, 1H), 3.08 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.95 (dd, *J* = 13.8, 9.3 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.9 (C_q), 171.7 (C_q), 171.3 (C_q), 169.1 (C_q), 169.0 (C_q), 169.0 (C_q), 136.2 (C_q), 135.7 (C_q), 134.9 (C_q), 130.8 (C_q), 129.0 (CH), 128.8 (C_q),

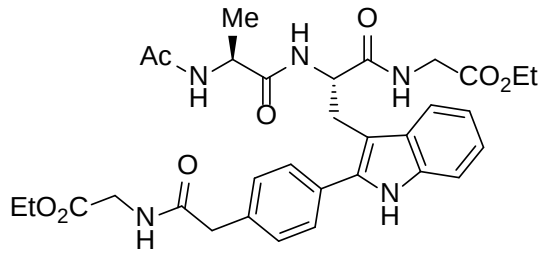
127.7 (CH), 121.1 (CH), 118.9 (CH), 118.4 (CH), 110.7 (CH), 107.2 (C_q), 60.2 (CH_2), 53.7 (CH), 53.5 (CH), 51.7 (CH_3), 48.3 (CH), 40.8 (CH_2), 36.4 (CH_2), 28.0 (CH_2), 22.4 (CH_3), 22.2 (CH_3), 17.7 (CH_3), 14.0 (CH_3).

IR (ATR): 3280, 1738, 1637, 1540, 1199, 1013, 738 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1265 (22) $[2M+Na]^+$, 644 (100) $[M+Na]^+$, 622 (96) $[M+H]^+$, 509 (9), 378 (5).

HR-MS (ESI): *m/z* calcd for $C_{32}H_{40}N_5O_8^+$ 622.2871, found 622.2877 $[M+H]^+$.

Synthesis of Ethyl Acetyl-*L*-alanyl-*L*-(*N*-phenylacetyl-glycine)tryptophyl-glycinate (102aw):



The general procedure D2 was followed using ethyl acetyl-*L*-alanyl-*L*-tryptophyl-glycinate (**101a**) (80 mg, 0.2 mmol) and (mesityl)(*N*-phenylacetyl-glycine)iodonium tosylate (**26w**) (191 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH: 1/4/0.4) yielded **102aw** (45 mg, 36%) as a pale white solid (m. p. = 135–137 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.08 (s, 1H), 8.50 (t, *J* = 5.9 Hz, 1H), 8.11 (t, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.97 (dd, *J* = 7.9, 7.0 Hz, 1H), 4.66 (ddd, *J* = 8.3, 7.2, 7.2 Hz, 1H), 4.19 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.03 (dq, *J* = 7.1, 1.7 Hz, 2H), 3.86 (d, *J* = 5.9 Hz, 2H), 3.70 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.60 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.56 (s, 2H), 3.31 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.10 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.79 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H).

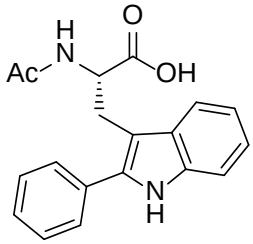
^{13}C NMR (126 MHz, d_6-DMSO): δ = 171.7 (C_q), 171.2 (C_q), 170.3 (C_q), 169.6 (C_q), 169.0 (C_q), 169.0 (C_q), 135.6 (C_q), 135.0 (C_q), 134.9 (C_q), 130.7 (C_q), 129.0 (CH), 128.8 (C_q), 127.7 (CH), 121.1 (CH), 118.9 (CH), 118.4 (CH), 110.7 (CH), 107.1 (C_q), 60.3 (CH_2), 60.2 (CH_2), 53.7 (CH), 48.3 (CH), 41.6 (CH_2), 40.8 (CH_2), 40.7 (CH_2), 27.9 (CH_2), 22.4 (CH_3), 17.6 (CH_3), 14.0 (CH_3), 13.9 (CH_3).

IR (ATR): 3280, 1738, 1640, 1526, 1373, 1196, 1010, 744 cm^{-1}.

MS (ESI) *m/z* (relative intensity) 1265 (12) $[2M+Na]^+$, 644 (100) $[M+Na]^+$, 622 (89) $[M+H]^+$, 509 (10), 378 (5), 242 (6).

HR-MS (ESI): *m/z* calcd for $C_{32}H_{40}N_5O_8^+$ 622.2871, found 622.2877 $[M+H]^+$.

Synthesis of *N*-acetyl-*L*-(phenyl)tryptophan (102gh):



The general procedure D3 was followed using *N*-acetyl-*L*-tryptophan (**101g**) (49 mg, 0.2 mmol) and diphenyl- iodonium tosylate (**26h**) (136 mg, 0.3 mmol). After 24 h, purification by column chromatography (*n*-hexane/EtOAc/MeOH/AcOH: 1/5/0.5/0.02) yielded **102gh** (55 mg, 85%) as a pale white solid (m. p. = 155–157 °C).

^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.14 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.74–7.67 (m, 3H), 7.48 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.35 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.08 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.99 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.55 (ddd, *J* = 8.1, 7.7, 7.7 Hz, 1H), 3.34 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.12 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.70 (s, 3H).

^{13}C NMR (126 MHz, d_6-DMSO): δ = 173.6 (C_q), 168.6 (C_q), 135.7 (C_q), 134.9 (C_q), 132.7 (C_q), 128.8 (C_q), 128.4 (CH), 127.8 (CH), 127.0 (CH), 121.1 (CH), 119.0 (CH), 118.4 (CH), 110.8 (CH), 108.0 (C_q), 53.6 (CH), 27.7 (CH_2), 22.4 (CH_3).

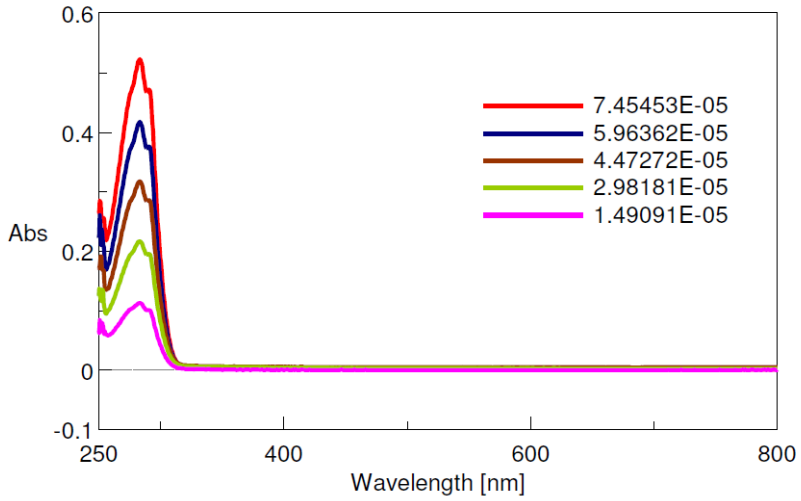
IR (ATR): 3280, 1715, 1650, 1523, 1448, 1237, 741 cm^{-1}.

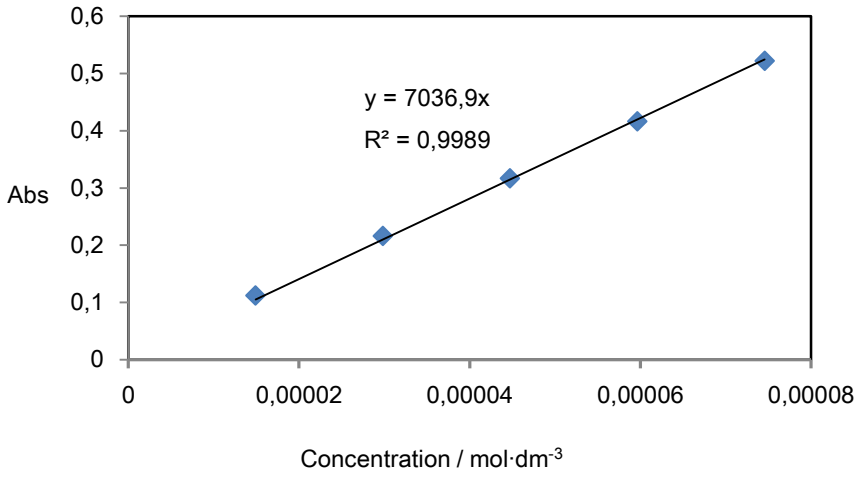
MS (ESI) *m/z* (relative intensity) 667 (44) $[2M+Na]^+$, 345 (100) $[M+Na]^+$, 323 (50) $[M+H]^+$, 264 (13), 206 (19).

HR-MS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O_3^+$ 323.1390, found 323.1396 $[M+H]^+$.

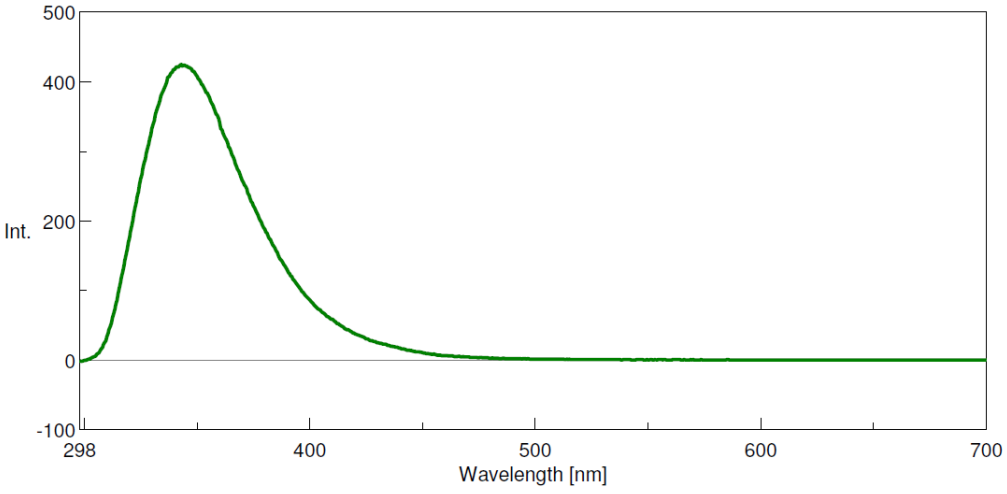
5.4.6 UV-Visible and Fluorescence Data for Arylated Tryptophan-Containing Peptides

UV-Visible spectroscopic analysis of compound **101a** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

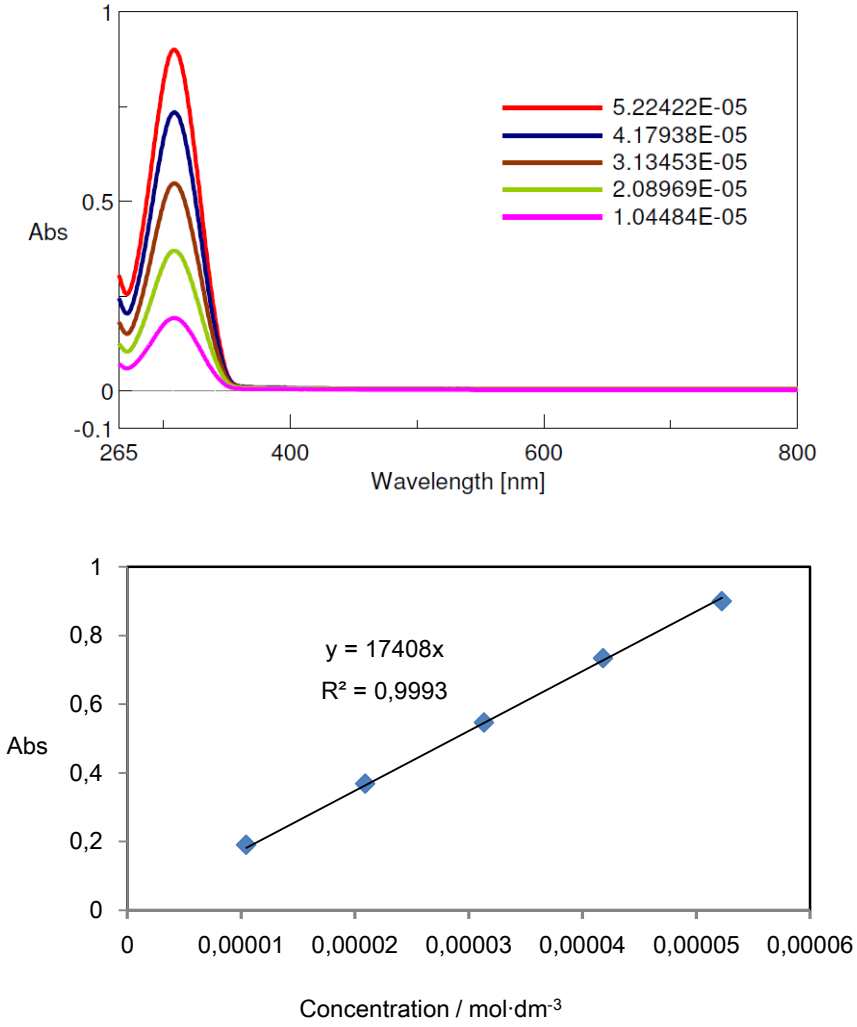




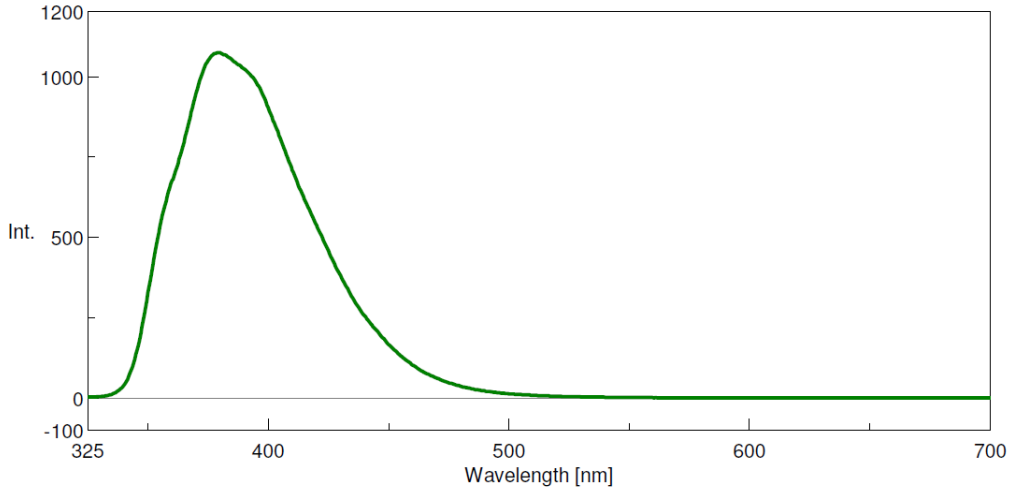
Fluorescence emission spectra of compound **101a** in DMSO (excitation at 283 nm).



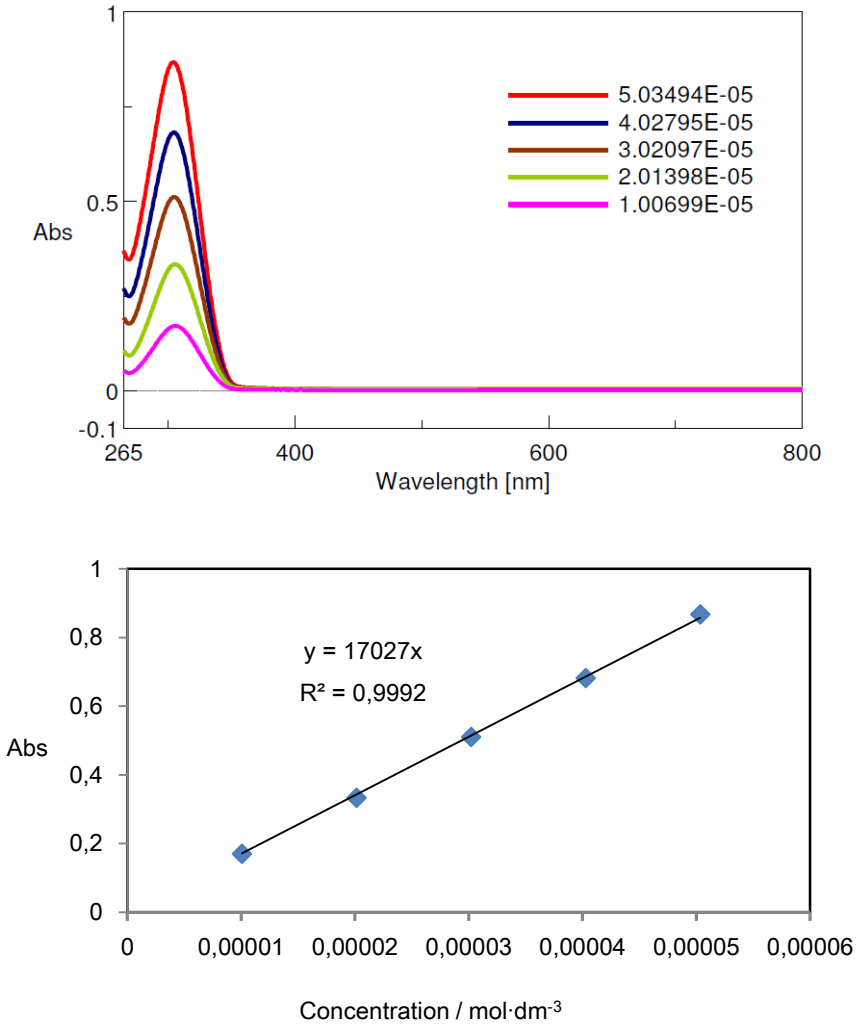
UV-Visible spectroscopic analysis of compound **102ah** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).



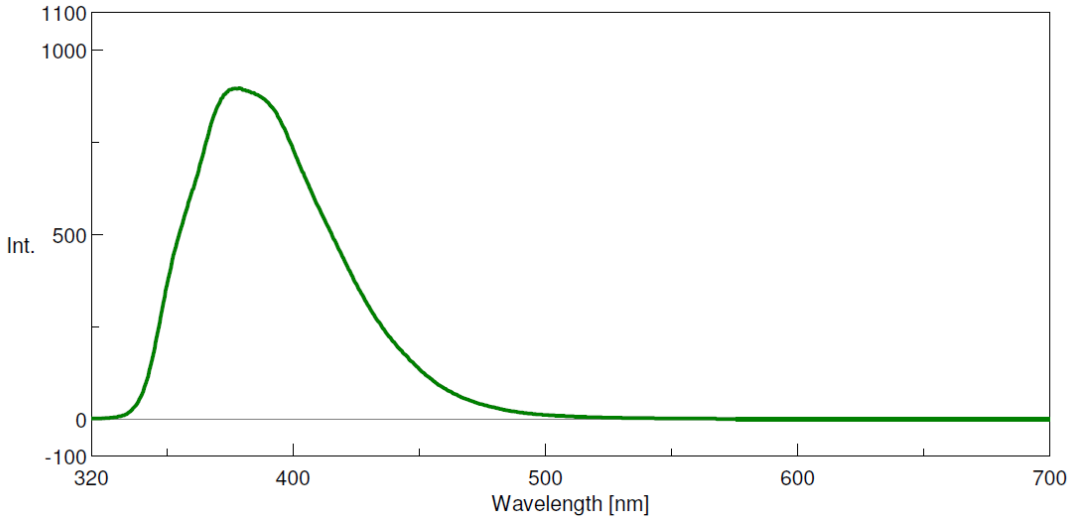
Fluorescence emission spectra of compound **102ah** in DMSO (excitation at 308 nm).



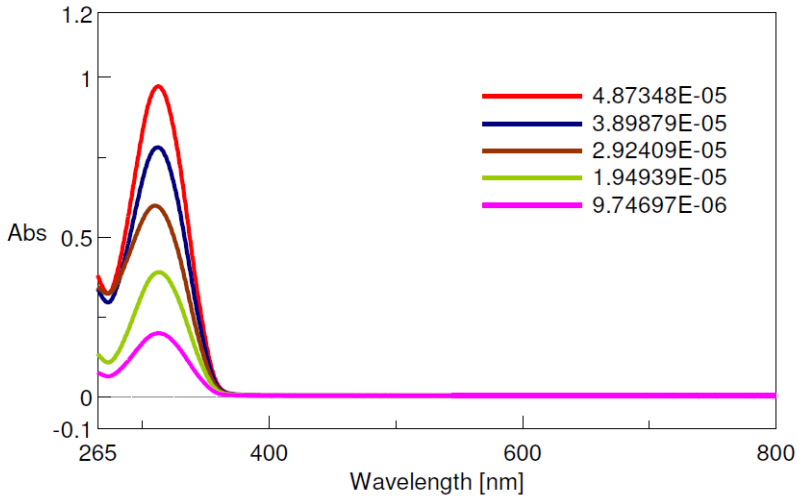
UV-Visible spectroscopic analysis of compound **102ai** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

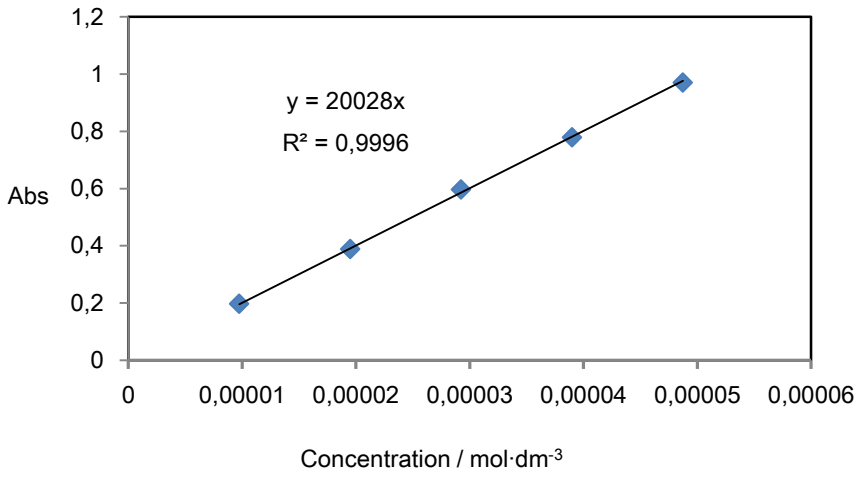


Fluorescence emission spectra of compound **102ai** in DMSO (excitation at 310 nm).

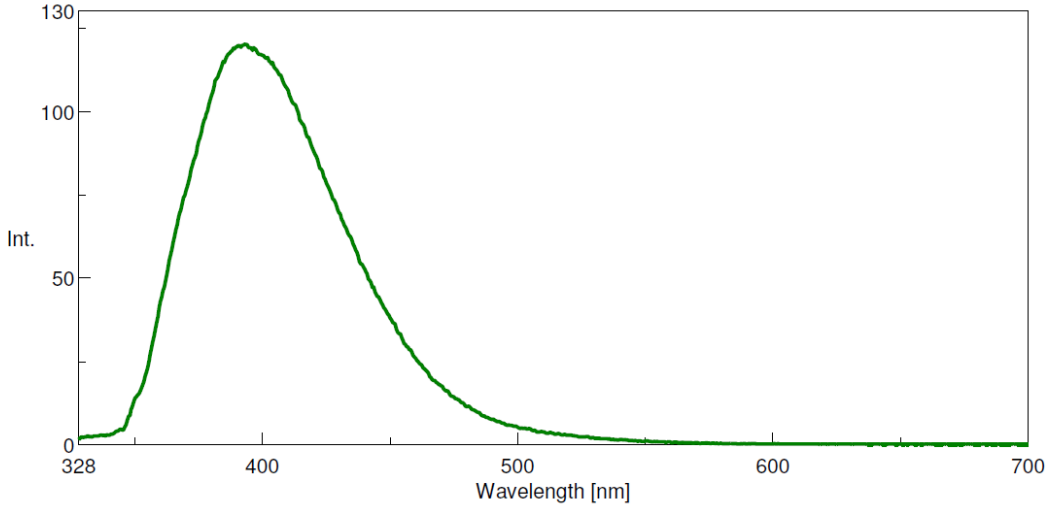


UV-Visible spectroscopic analysis of compound **102aj** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

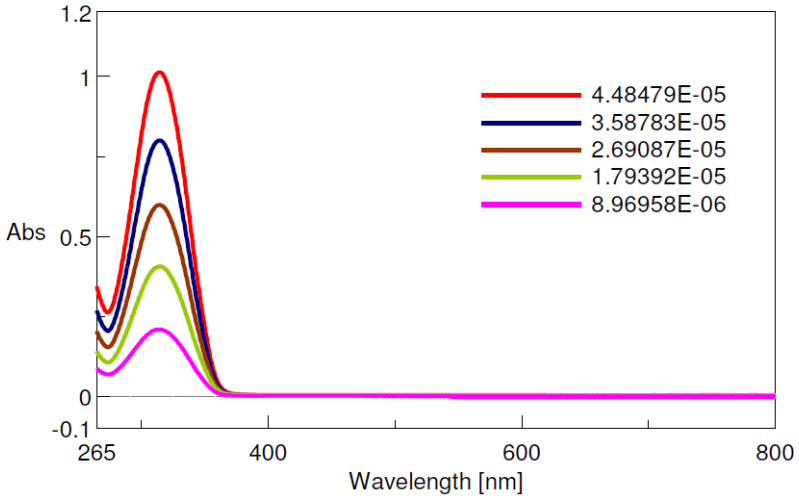


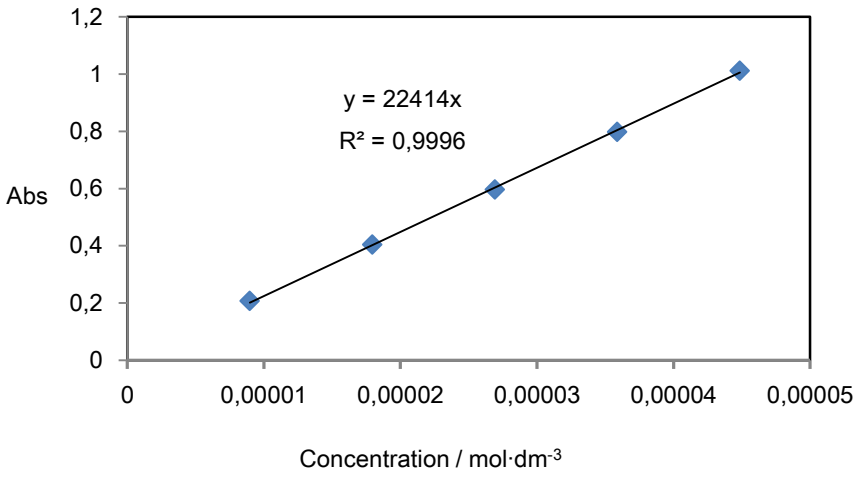


Fluorescence emission spectra of compound **102aj** in DMSO (excitation at 313 nm).



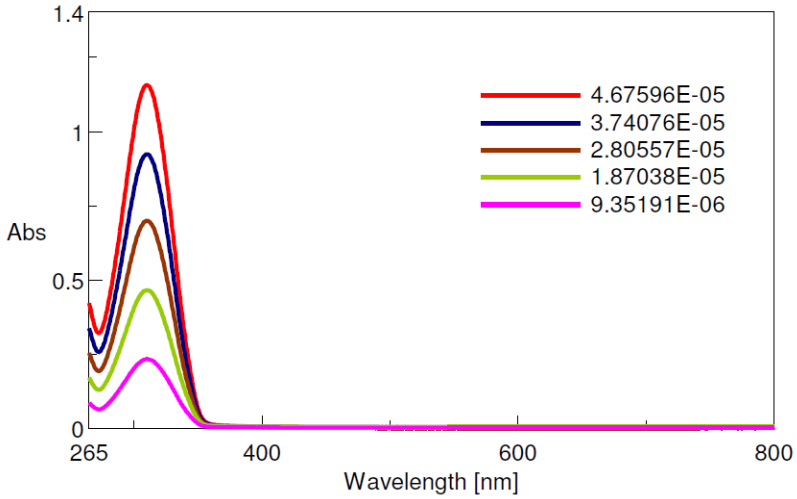
UV-Visible spectroscopic analysis of compound **102ak** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

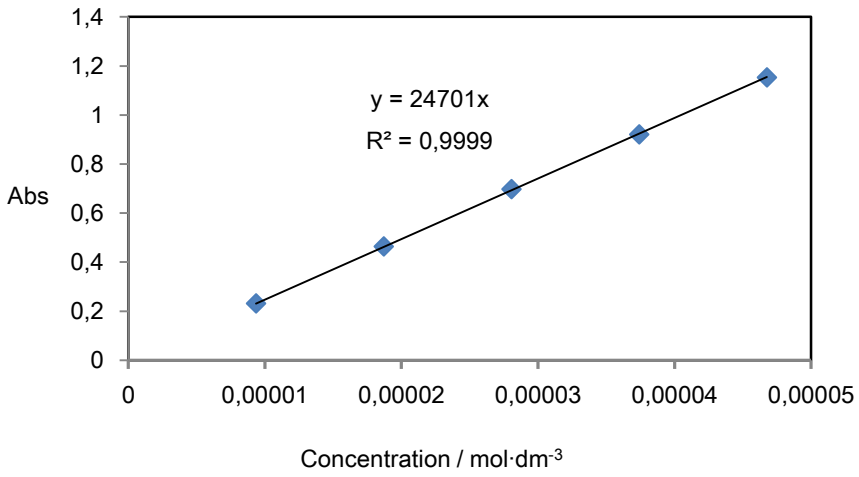




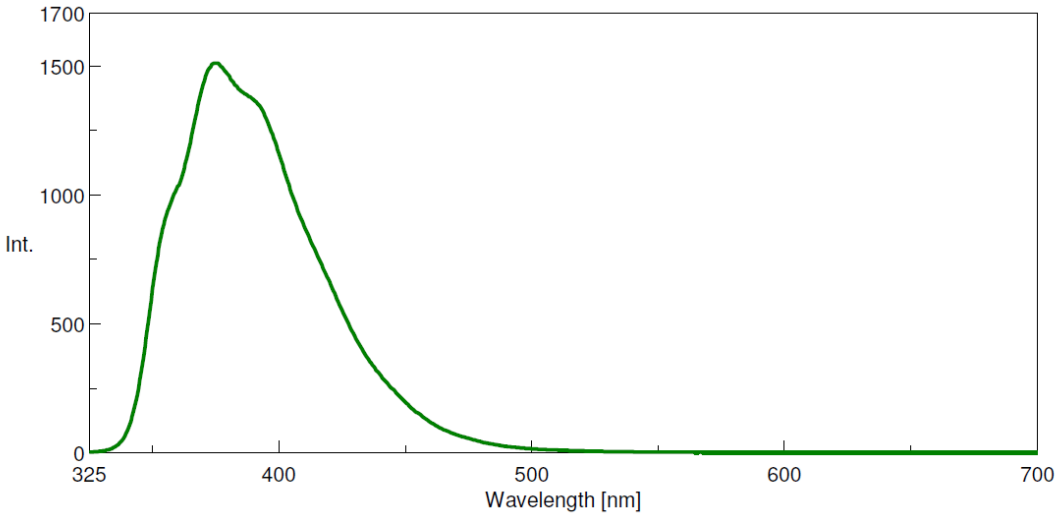
No fluorescence emission of the peptide **102ak** in DMSO was detected.

UV-Visible spectroscopic analysis of compound **102al** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

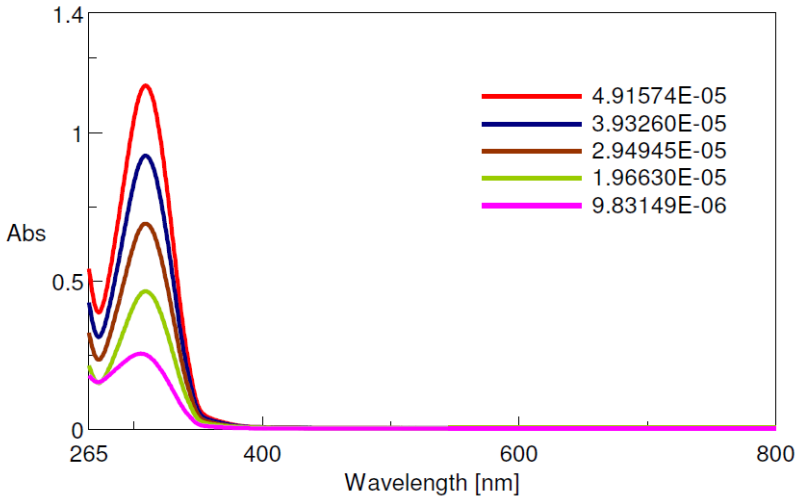


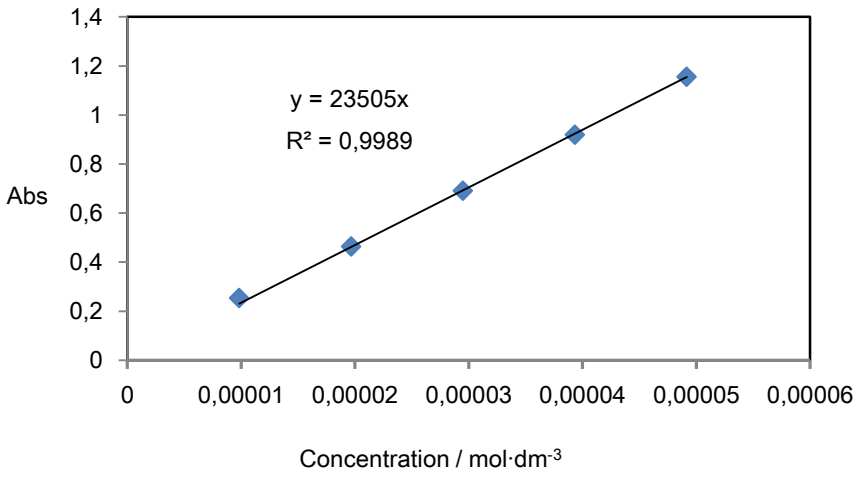


Fluorescence emission spectra of compound **102al** in DMSO (excitation at 311 nm).

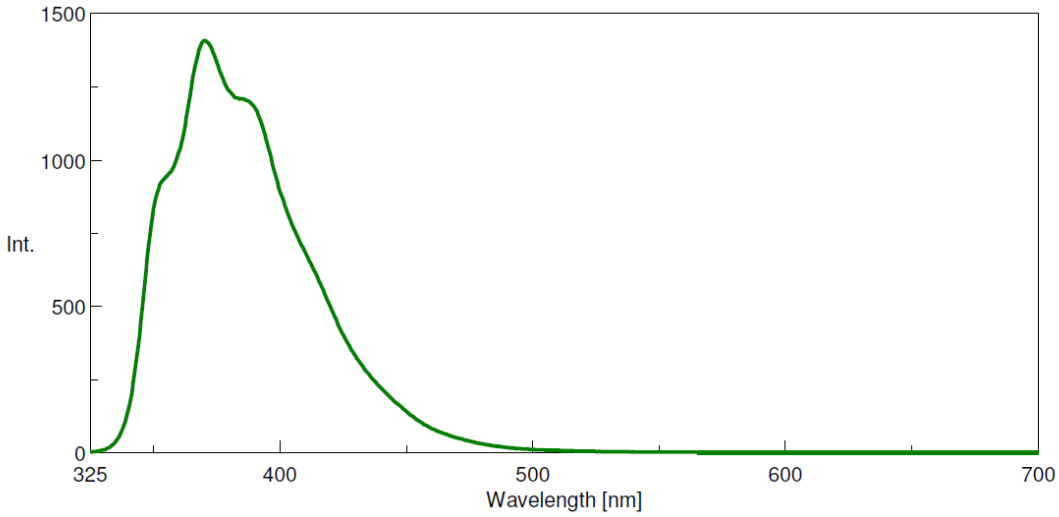


UV-Visible spectroscopic analysis of compound **102ag** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

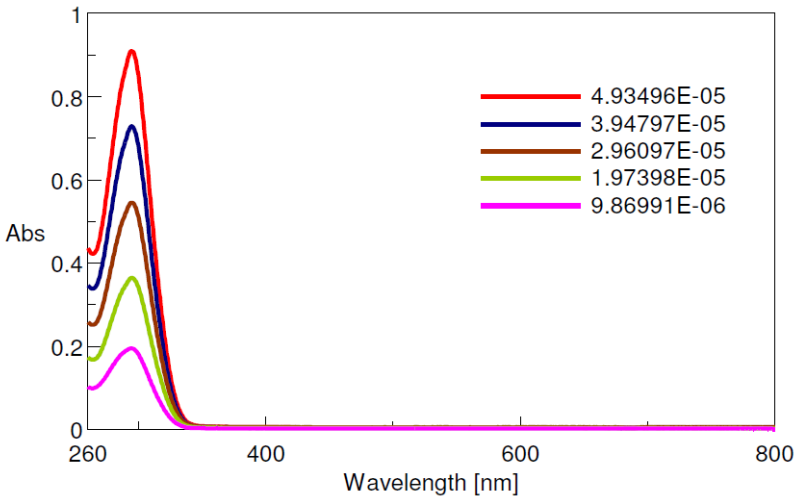


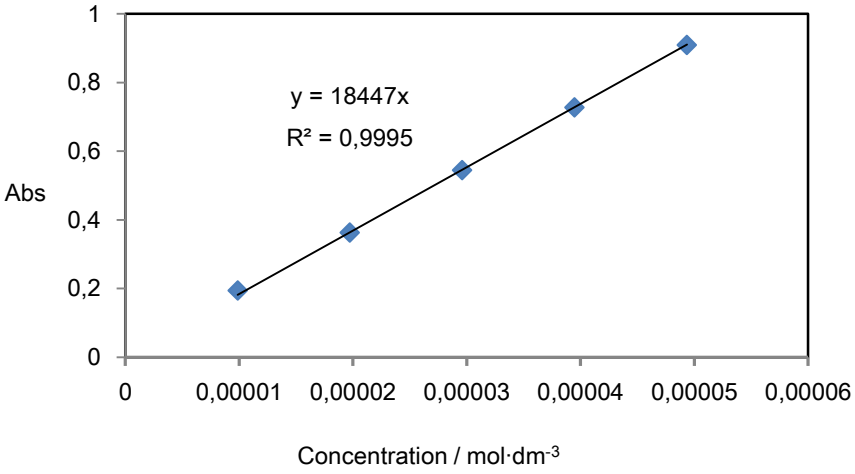


Fluorescence emission spectra of compound **102ag** in DMSO (excitation at 310 nm).

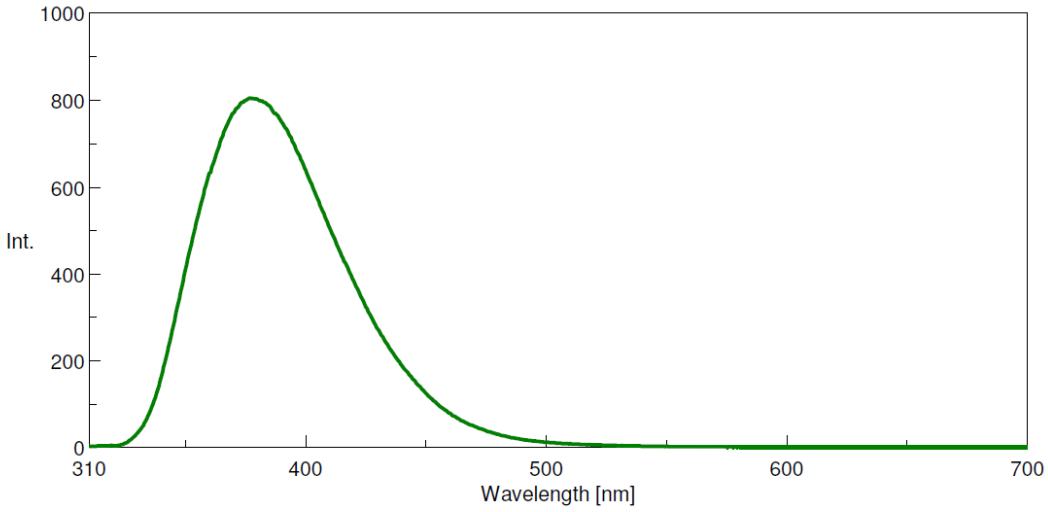


UV-Visible spectroscopic analysis of compound **102am** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

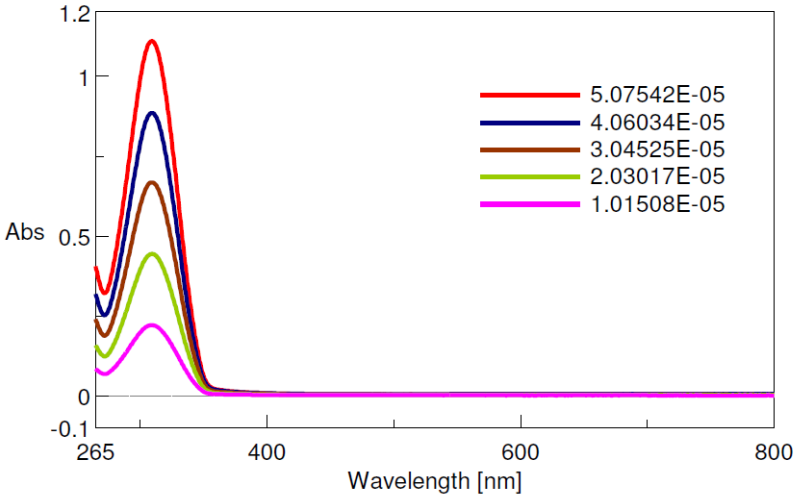


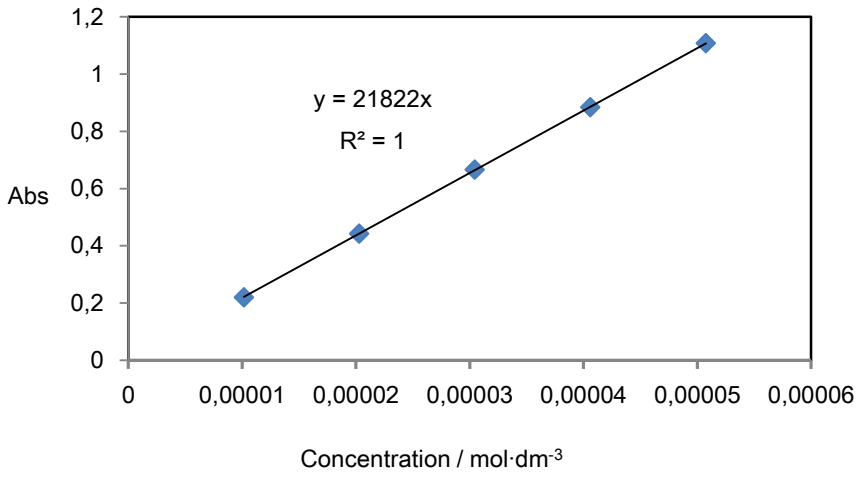


Fluorescence emission spectra of compound **102am** in DMSO (excitation at 295 nm).

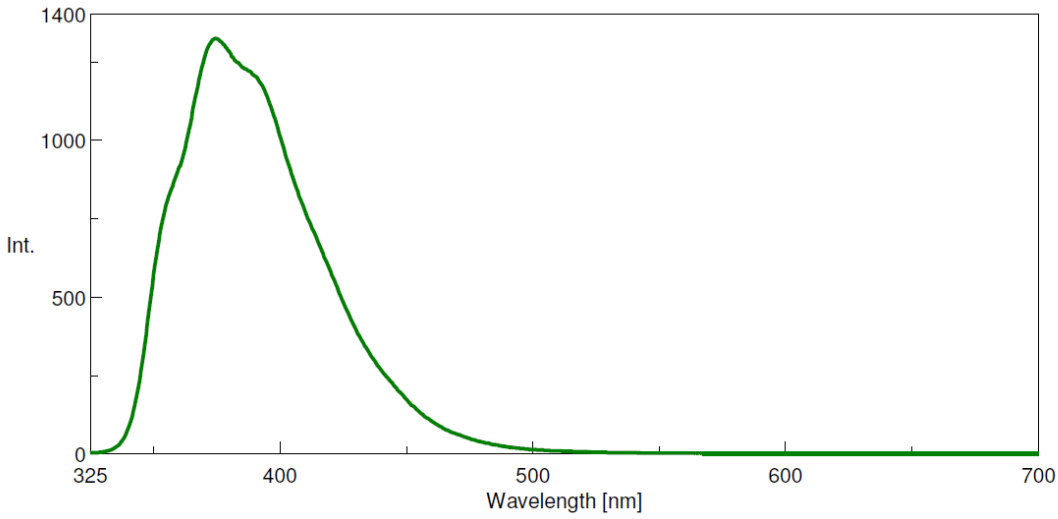


UV-Visible spectroscopic analysis of compound **102as** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

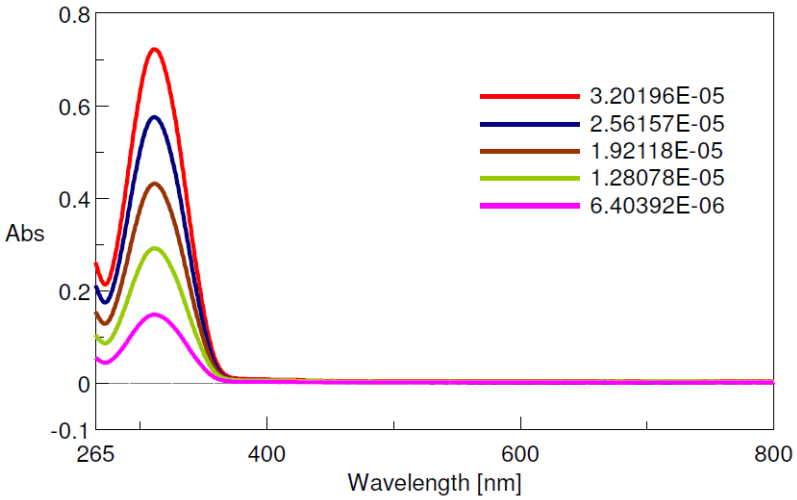


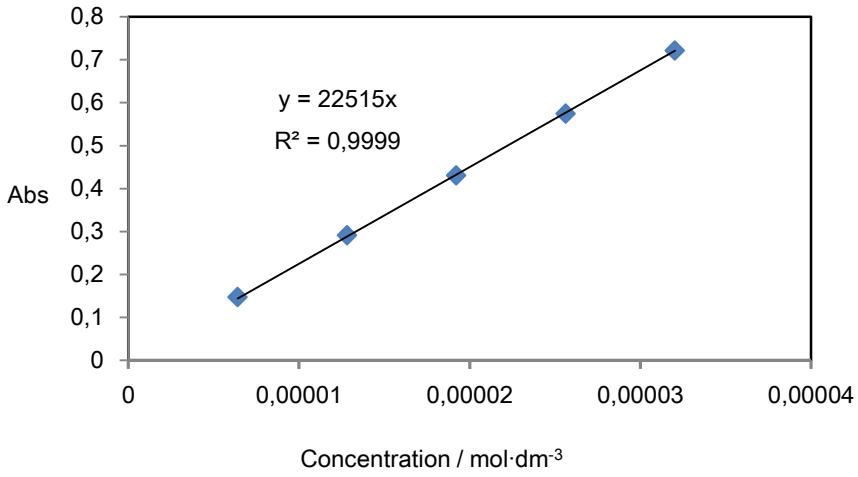


Fluorescence emission spectra of compound **102as** in DMSO (excitation at 310 nm).

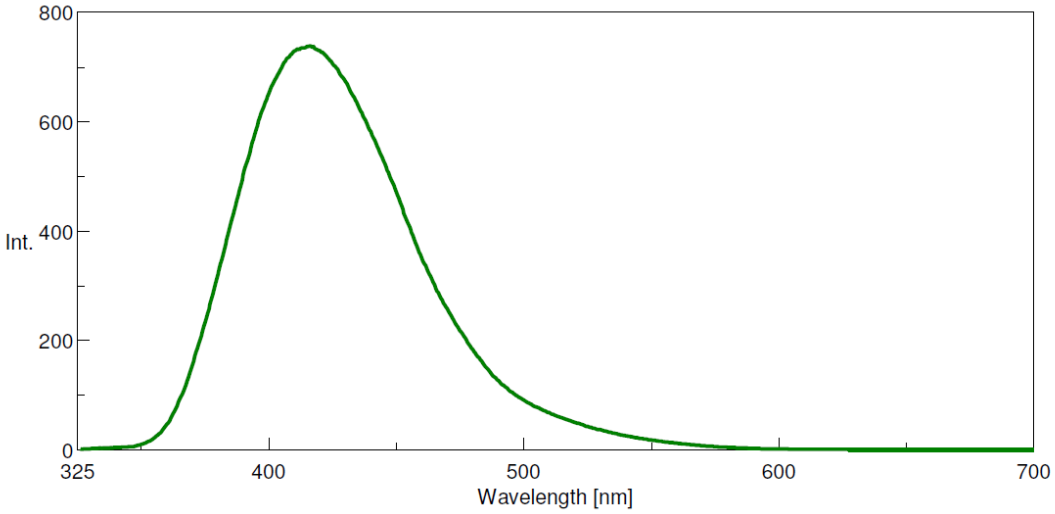


UV-Visible spectroscopic analysis of compound **102at** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

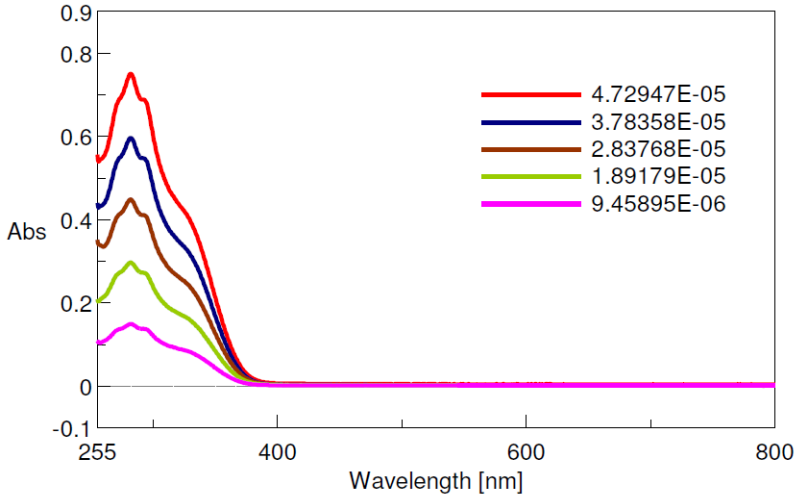


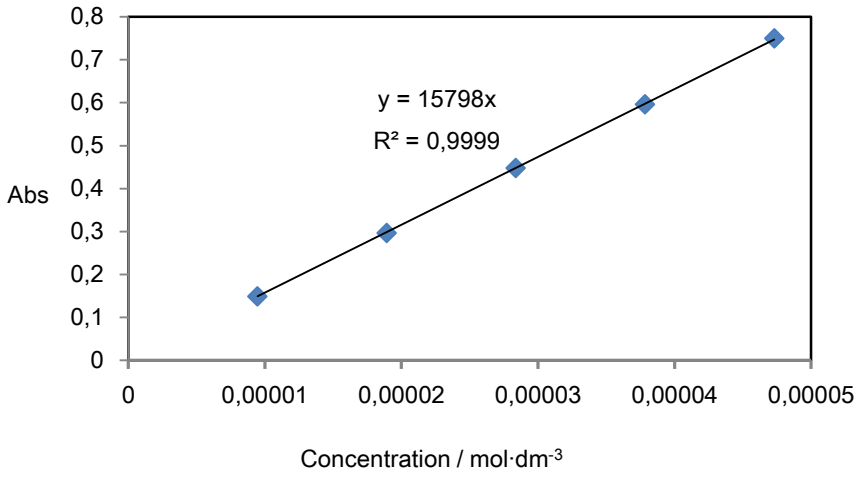


Fluorescence emission spectra of compound **102at** in DMSO (excitation at 312 nm).

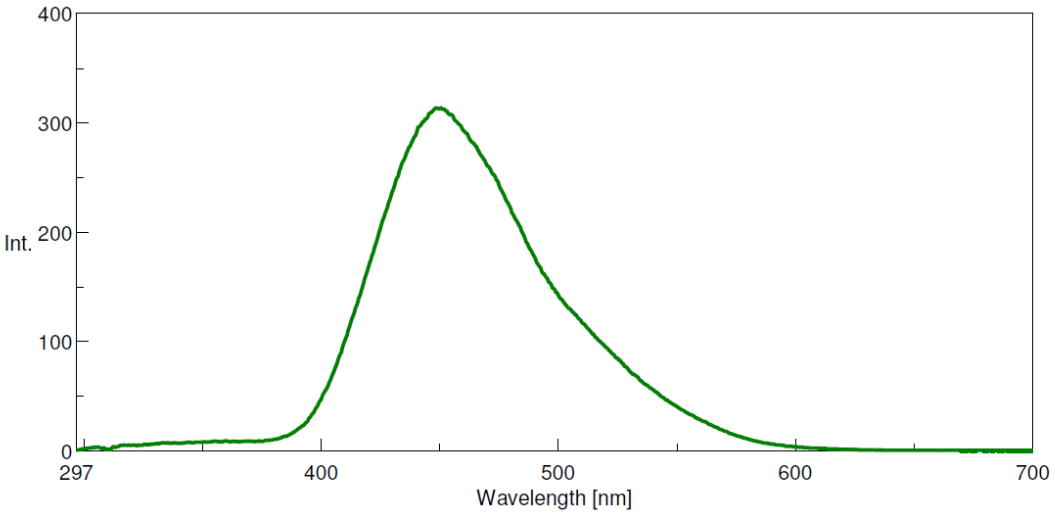


UV-Visible spectroscopic analysis of compound **102au** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

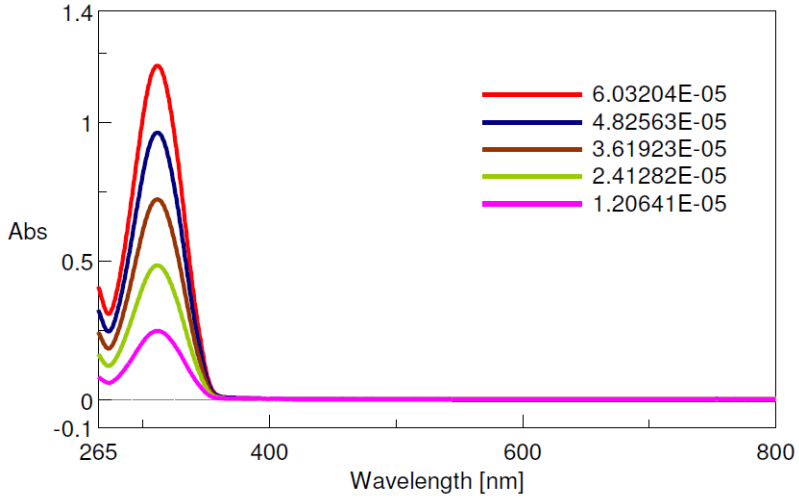


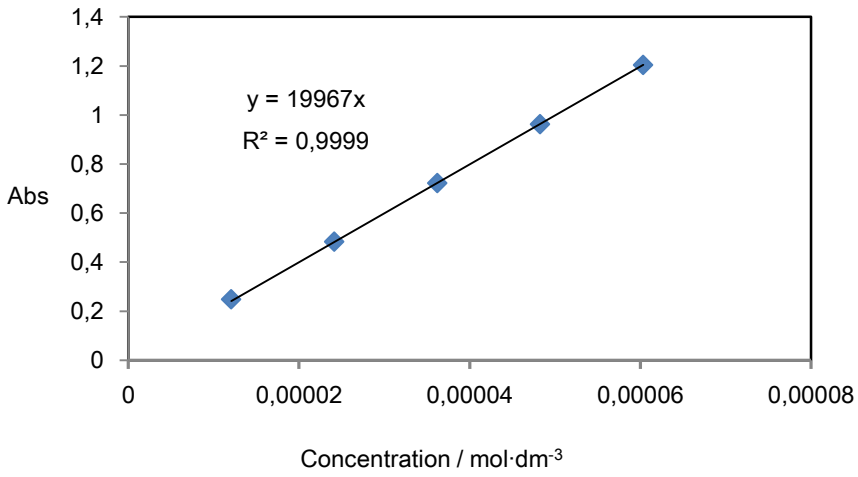


Fluorescence emission spectra of compound **102au** in DMSO (excitation at 282 nm).

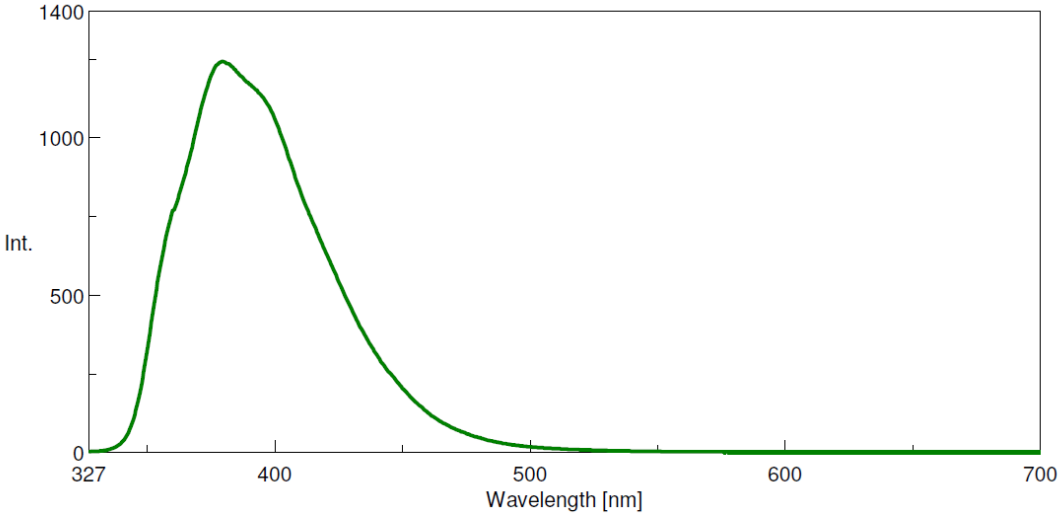


UV-Visible spectroscopic analysis of compound **102av** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).

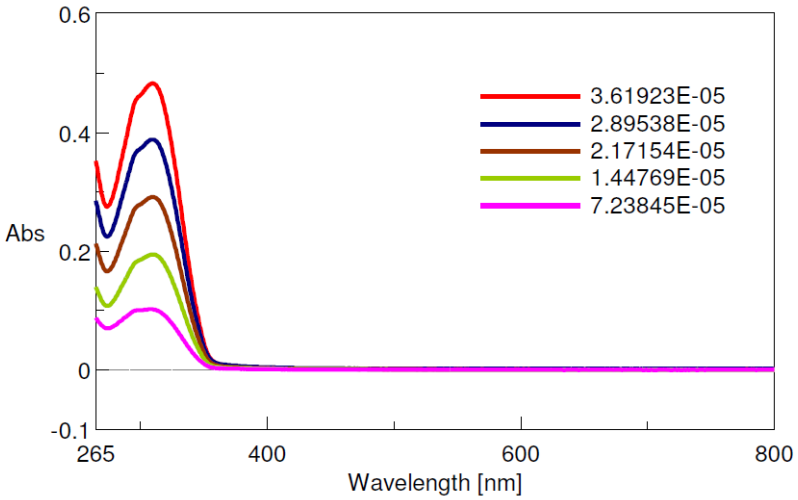


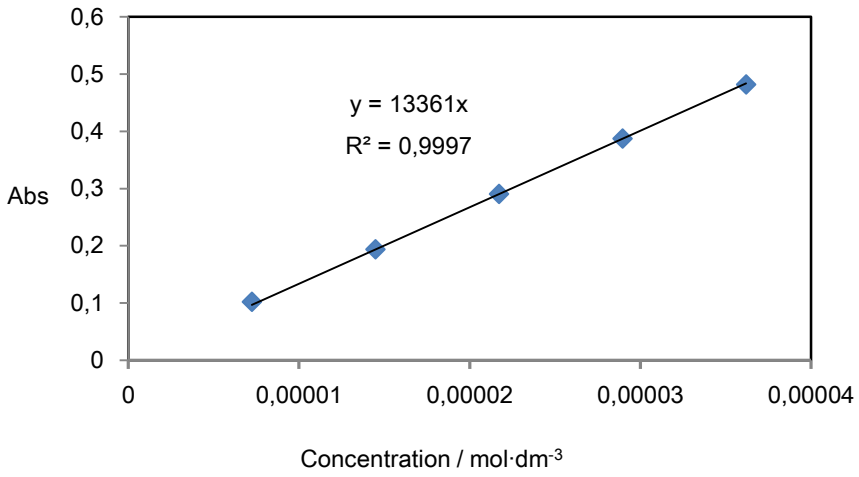


Fluorescence emission spectra of compound **102av** in DMSO (excitation at 311 nm).

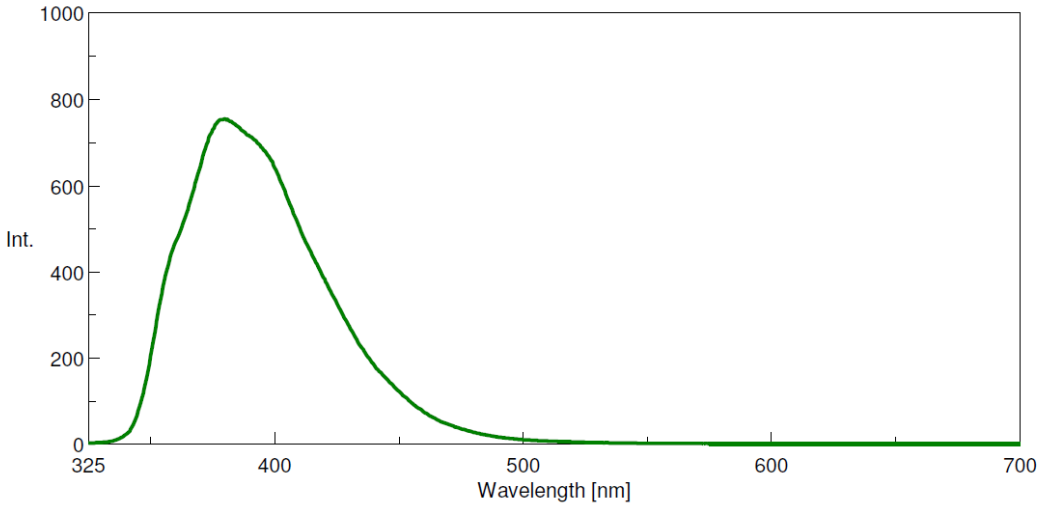


UV-Visible spectroscopic analysis of compound **102aw** in DMSO (the concentration range is shown in the figure key, in mol·dm^{-3}).





Fluorescence emission spectra of compound **102aw** in DMSO (excitation at 310 nm).



6 List of Abbreviations

Abs	absorbance
Ac	acetyl
Ala	alanine
AMLA	ambiphilic metal ligand activation
Arg	arginine
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2'-bipyridine
BTMG	*tert*-butyl-tetramethylguanidine
Bu	butyl
Bz	benzoyl
°C	degree Celsius
CAPT	chiral anion phase transfer
cat.	catalytic
Cbz	benzyloxycarbonyl
CMD	concerted metalation deprotonation
conv.	conversion
Cys	cysteine
δ	chemical shift
DCE	1,2-dichloroethane
DG	directing group
DMF	dimethylformamide
DPE-Phos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dtbpy	2,6-di-*tert*-butylpyridine
E^+	electrophile
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
et al.	*et alia*
Fmoc	fluorenylmethyloxycarbonyl
GC-MS	gas chromatography-mass spectrometry
gem	geminal
Gln	glutamine
h	hour
Het	hetero
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
His	histidine
HMBC	heteronuclear multiple bond correlation
HR	high resolution

HPLC	high-performance liquid chromatography
i.e.	id est
Imes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
Int.	intensity
IR	infrared spectroscopy
J	coupling constant
KIE	kinetic isotope effect
LED	light-emitting diode
Lys	lysine
m-	*meta*-
m	multiplett
M	molar
mCPBA	*meta*-chloroperoxybenzoic acid
MEHQ	hydroquinone monomethyl ester
Met	methionine
Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimol
m. p.	melting point
MTBE	methyl *tert*-butyl ether
MW	microwave
m/z	mass to charge ratio
n-	*normal*-
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
o-	*ortho*-
Oct	octyl
OTf	triflate
OTs	tosylate
p-	*para*-
P	peptide
PdNPs	palladium nanoparticles
Ph	phenyl
Phe	phenylalanine
Piv	pivaloyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine

R	rest
SEM	[2-(trimethylsilyl)ethoxy]methyl
Ser	serine
SET	single electron transfer
SPPS	solid-phase peptide synthesis
t	*tert*
Temp.	temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	trifluoroacetate
THF	tetrahydrofuran
TM	transition metal
TMS	trimethylsilyl
Trp	tryptophan
Trt	trityl
Ts	tosyl
Tyr	tyrosine
wt%	weight percentage

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L. Ackermann, C. Kornhaaß, **Y. Zhu**, "*Palladium-Catalyzed Direct C–H Bond Alkynylations of Heteroarenes Using gem-Dichloroalkenes*" *Org. Lett.* **2012**, *14*, 1824–1826.

Date, Place..... Signature: .....