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Zn-Catalyzed Nicotinate-Directed Transamidations in Peptide Synthesis

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ABSTRACT

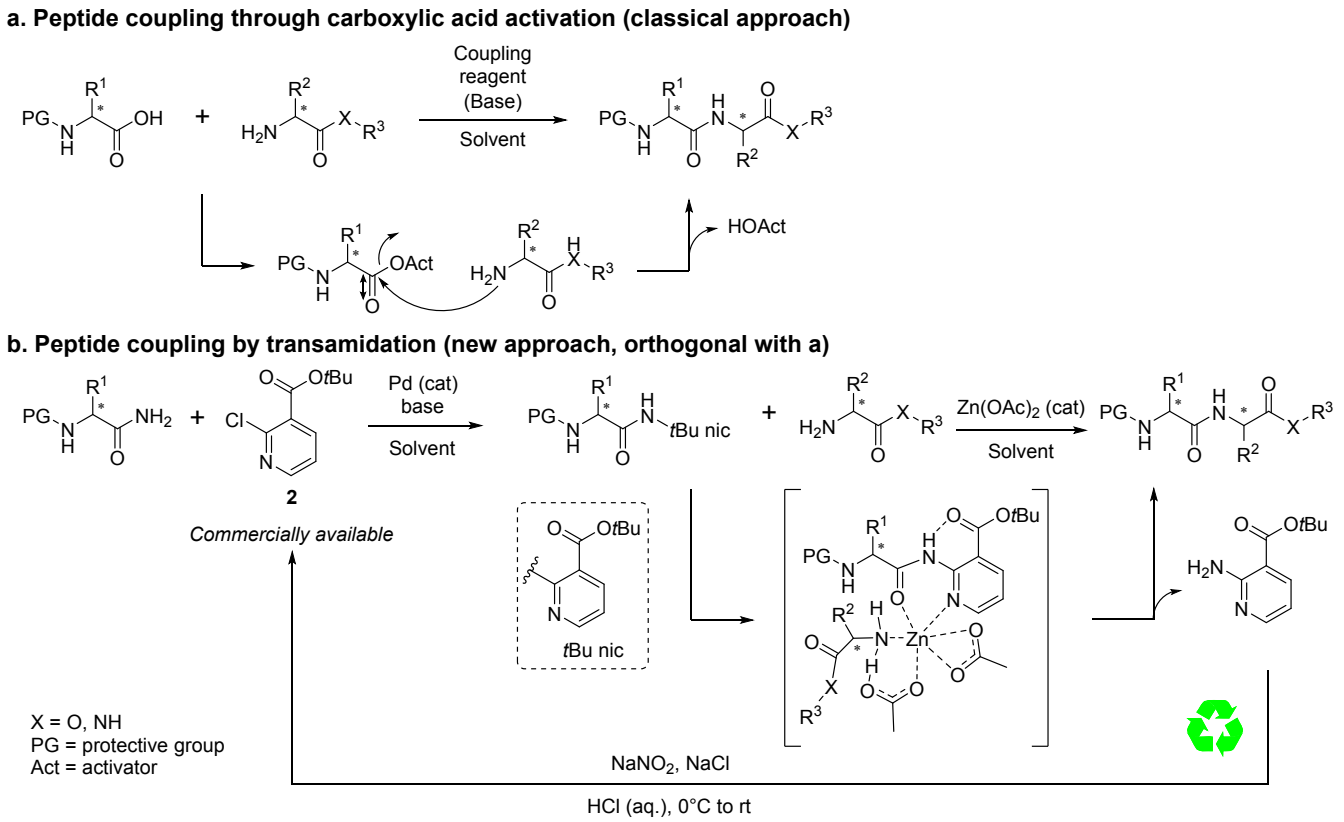
A chemoselective and catalytic transamidation for peptide synthesis is described. Transamidation under Zn catalysis is chemoselectively achieved by amino acid amide/peptidic amide derivatization with a *tert*-butyl nicotinate (*t*Bu nic) directing group. The directing group could be easily introduced on protected amino acid amides *via* Pd-catalyzed amidation with *t*Bu 2-chloronicotinate (*t*Bu nicCl). Under standard peptide coupling/deprotection conditions, the *t*Bu nic equipped amino acid amides proved to be fully inert allowing to be easily built-in in complex molecules. The disclosed method was evaluated in the synthesis of diverse dipeptides, in dipeptide segment coupling, in side chain modification of a solid supported tetra/pentapeptide, and in the macrocyclization of a heptapeptide.

Keywords: Amide cleavage, Transamidation, Directing group, Peptide, Amino acid amide

INTRODUCTION

The amide functionality is of utmost importance in both biology and chemistry. Molecules sustaining life, such as peptides and proteins, are composed of repeating amino acid monomers connected by amide bonds. Their significance as part of therapeutic compounds is demonstrated by the list of FDA-approved drugs of 2018 in which 69% features an amide entity.[1] Consequently, formation of this functional group is considered to be among the most executed transformations in organic chemistry,[2] with a major application in the synthesis of peptides and peptidomimetics. In the last decades, chemists have made immense efforts to form amide bonds in an efficient and selective manner. Direct acylation of an amine with an *in situ* activated carboxylic acid[2-3] remains the most common procedure and accounts for 16% of all reactions in pharmaceutical synthesis (Scheme 1a).[2d,4] This manifests in a well-established catalog of so-called coupling reagents. Nevertheless, amide formation has yet to overcome the inherent limitations associated with these coupling reagents, such as elevated prices, potentially explosive properties and (super)stoichiometric amounts.[2d-f] Furthermore, the carboxylic acid activation is still linked to risks, like enolization and oxazolone formation, resulting in the epimerization of chiral centers.[2b] In certain cases, such as segment coupling or macrocyclization, activation of a single carbamate *N*-protected amino acid is no longer possible which greatly complicates the couplings.[2b] To address these issues new strategies focusing on non-classical approaches for amide synthesis have been introduced,[2c] for instance, through amine activation[5] or *via* alternative functional groups.[6] In the latter strategy major advances involve the α-ketoacid-hydroxylamine-ligation, introduced by Bode,[6d, 6f] and the umpolung strategy of Johnston.[6a, 6g-k]

Scheme 1. Peptide synthesis: (a) Traditional approach: carboxylic acid activation and (b) New approach: Zn-catalyzed nicotinate-directed transamidation.



Amides themselves have rarely been considered as a carboxylic acid surrogate. Given the prevalence of the amide functional group, transamidations with amines are potentially interesting reactions to obtain amides with other substitution patterns. However, these reactions are faced with two main challenges:[7] i) intrinsic stability and poor carbonyl electrophilicity of amides, and ii) the thermodynamically neutral character of these transformations involving an amine as both nucleophile and by-product as illustrated by the work of Gellman and Stahl.[8] Following the work of Bigg and Bertand reporting transamidations with unfunctionalized amides and amines and (super)stoichiometric $AlCl_3$,[9] various efficient preparative catalytic transamidations at higher temperature have been published.[10] Recent important advances involve amide activation prior to transamidation, typically allowing milder conditions and a broader scope in both reaction partners. Garg and Szostak reported Ni- and Pd-catalyzed transamidations of tertiary amides by *N*-activation of secondary amides through *N*-Bocylation or *N*-Tosylation.[11-14] In some cases transition metal free transamidation reactions of *N*-activated secondary amides are possible.[15] By deprotonation of

the amine nucleophile with LiHMDS also unactivated tertiary amides have recently been used.[16] Mild transamidation on secondary amides, by activation of primary amides is to the best of our knowledge still unknown. The cleavage of amides in complex and sensitive molecules such as peptides has been established in reversible native chemical ligation (*N*→*S* acyl shift).[17] Nonetheless, a direct transamidation that introduces an additional degree of orthogonality in peptide synthesis, e.g. for late-stage modification, segment coupling and macrocyclization, would be exceedingly valuable.[18,19]

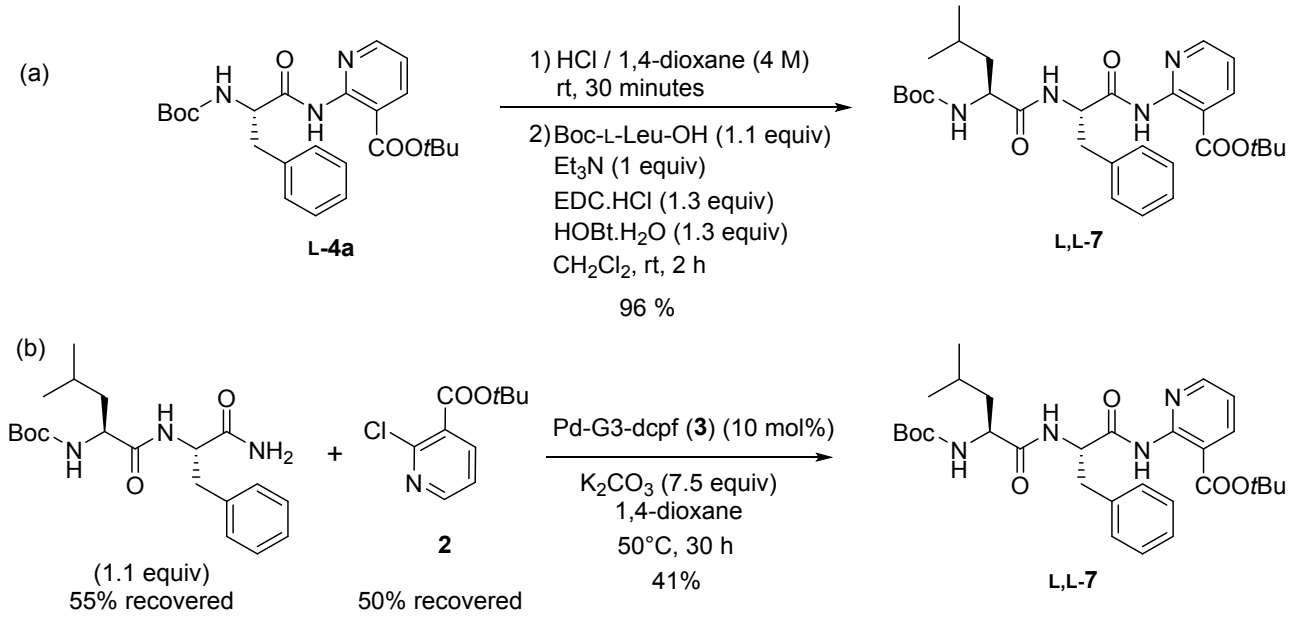
Recently our group introduced a general protocol for primary amide esterification *via* derivatization with a *t*Bu nicotinate (*t*Bu nic) directing group (DG).[20] The *t*Bu nic is easily introduced through a Pd-catalyzed amidation on a primary amide with commercially available *t*Bu 2-chloronicotinate (**2**) (Table 1). Subsequently, the amide bond is cleaved with alcohols by Zn catalysis. The activation mechanism involving *t*Bu nic amide chelation by a Zn catalyst is biomimetic with metalloproteases. DGs are commonly used for C-H bond functionalization, but not for amide activation.[21] In the esterification reaction, *t*Bu 2-aminonicotinate is released. This by-product can be easily transformed into reactant **2** through functional group interconversion involving a diazotization reaction.[20] In this work, we disclose an unprecedented mild transamidation reaction to be used in peptide synthesis which is orthogonal with classical methods *via* transamidation of *N*-protected *N'*-*t*Bu nic amino acid amides, *N*-activated primary amides, with amino acid esters/amides (Scheme 1b).

Results and discussion

Boc-protected directing group-bearing amino acid amides **4** were synthesized *via* our previously developed Pd-catalyzed amidation protocol of primary amides with commercially available *t*Bu 2-chloronicotinate (*t*Bu nicCl) (**2**), based on a Buchwald Pd-G3-dcpf precatalyst with K_2CO_3 or Cs_2CO_3 as base in 2-MeTHF or dioxane at 40-50°C.[20,22] This mild method proved generally applicable for amino acid amides, also those with protected nucleophiles in the side chain, and can even be applied on peptides (Table 1).[20] Sometimes the use of K_2CO_3 is required to avoid epimerization and a larger excess of base is beneficial for the reaction rate ("base effect").[23] $Pd(OAc)_2$ in combination with commercially available

Xantphos as ligand could also be used to introduce the directing group provided a higher reaction temperature (90°C) is applied.[20] In this case higher boiling 1,4-dioxane was selected as solvent. Though good yields were generally obtained only for some Boc-AA-NH_2 **1** (**L-4d** and **L,L-4n**) significant epimerization could be avoided (see Supporting Information; Table S13). Pd-G3-dcpf precatalyst which can be used at 40-50°C is therefore generally preferred as it retains the chiral information. Interestingly, the compounds of type **4** proved to be bench stable and the *t*Bu nic amide functionality remains untouched under classical peptide coupling conditions providing full orthogonality as exemplified for the synthesis of substrates **L,L-7**, **L,L-8**, **13**, **15.HCl** used in the transamidations (see Supporting Information; e.g. assembly of **L,L-7** in Scheme 2a). When **L,L-7** was prepared *via* Pd-catalyzed amidation of Boc-L-Leu-L-Phe-NH_2 with *t*Bu nicCl (**2**) under the standard conditions a lower yield was obtained (Scheme 2b). Interestingly, under these conditions without further optimization no epimerization was observed and unreacted amide was recovered providing a good mass balance. Amides also occur in the side chain of amino acids and therefore we tested whether the directing group could be introduced on L-glutamine. This is particularly challenging considering the presence of a free carboxylic acid. Boc-L-Gln(NH-*t*Bu nic)-OH (**L-4o**) could be obtained in 60% when the $Pd(OAc)_2$ / Xantphos precatalyst system was used (Scheme 3). In this case Buchwald Pd-G3-dcpf precatalyst did not provide any reaction product **L-4o.**

Scheme 2. Synthesis of *t*Bu nic-functionalized dipeptide **L,L-7** *via* application of Boc-L-Phe-*t*Bu nic **L-4a** in classical peptide synthesis (a) and Pd-catalyzed amidation of Boc-L-Leu-L-Phe-NH_2 with *t*Bu NicCl (**2**) (b).



Scheme 3. Synthesis of Boc-L-Gln(NH-*t*Bu nic)-OH (**L-4o**) *via* Pd-catalyzed amidation of Boc-L-Gln-OH with *t*Bu NicCl (**2**).

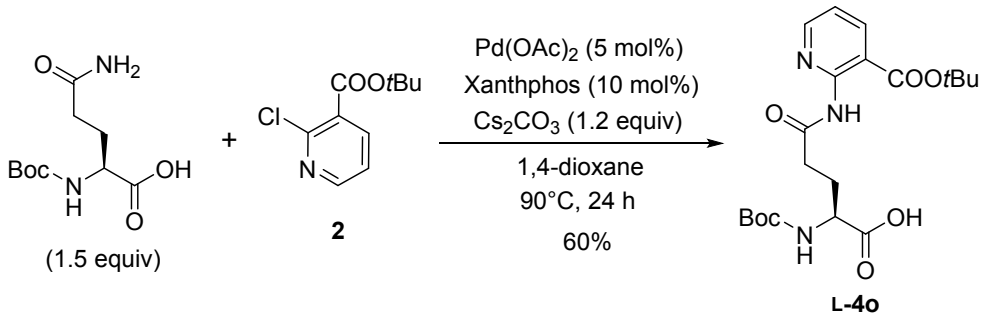
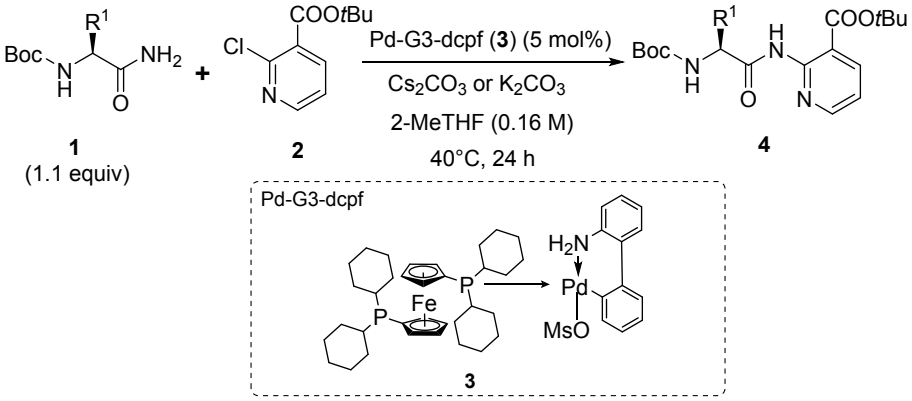


Table 1. Synthesis of *N*-Boc *N'*-*t*Bu nic amino acid amides (**4**) *via* Pd-catalyzed amidation of *N*-Boc amino acid / peptidic amides (**1**) with *t*Bu nicCl (**2**).



Entry	Boc-AA-NH-*t*Bu nic **4**	Base	Equivalents of base	Yield [%][a]	%ee[e]
1	Boc-L-Phe-NH-*t*Bu nic **L-4a**	K_2CO_3	7.5	93[b]	99
2	Boc-L-Ala-NH-*t*Bu nic **L-4b**	K_2CO_3	7.5	71[b]	100
3	Boc-L-Tyr(*t*Bu)-NH-*t*Bu nic **L-4c**	K_2CO_3	7.5	94[b]	100
4	Boc-L-Pro-NH-*t*Bu nic **L-4d**	Cs_2CO_3	1.2	80	100
5	Boc-L-Met-NH-*t*Bu nic **L-4e**	K_2CO_3	7.5	93[b,c]	100
6	Boc-βAla-NH-*t*Bu nic **4f**	Cs_2CO_3	2	99	-
7	Boc-Gly-NH-*t*Bu nic **4g**	Cs_2CO_3	1.2	83	-
8	Boc-L-Val-NH-*t*Bu nic **L-4h**	Cs_2CO_3	2	96	96
9	Boc-L-Ile-NH-*t*Bu nic **L-4i**	Cs_2CO_3	2	82	100[f]
10	Boc-L-Ser(*t*Bu)-NH-*t*Bu nic **L-4j**	K_2CO_3	6	72[b]	99

11	Boc-L-Lys(Boc)-NH-*t*Bu nic **L-4k**	Cs_2CO_3	1.2	79	100
12	Boc-L-Cys(*t*Bu)-NH-*t*Bu nic **L-4l**	K_2CO_3	7.5	89[b]	100
13	Boc-L-His(trt)-NH-*t*Bu nic **L-4m**	Cs_2CO_3	1.2	56[d]	98
14	Boc-L-Pro-L-Leu-Gly-NH-*t*Bu nic **L,L-4n**	Cs_2CO_3	2	99	100[f]

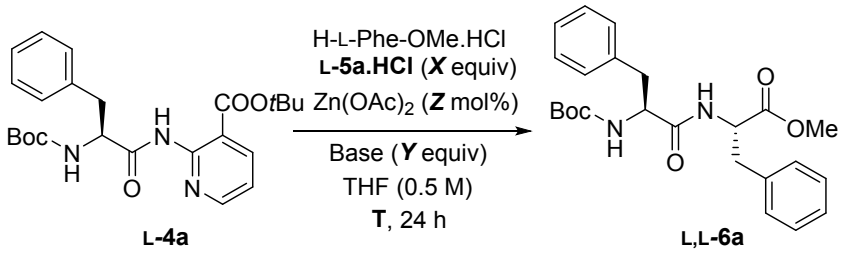
[a] Isolated yield. [b] Pd-G3-dcpf (10 mol%) in 1,4-dioxane, 50°C, 30 h. [c] 60°C. [d] Pd-G3-dcpf (10 mol%), 16 h, 50v/v% 2-MeTHF/DMF, 16 h. [e] %ee measured using HPLC with *n*-hexane:*i*-propanol on a Diacel Chiralpak IA column. [f] %de calculated based on ^{1}H NMR analysis.

As model system for the optimization of the transamidation, the synthesis of Boc-L-Phe-L-Phe-OMe (**L,L-6a**) from Boc-L-Phe-NH-*t*Bu nic (**L-4a**) and H-L-Phe-OMe (**L-5a**) was selected. The reaction conditions of the alcoholysis, previously developed in our laboratories, were used as a starting point.[20] A solvent screen revealed THF to be the most suitable solvent with respect to solubility and conversion (Table S1). With 10 mol% $Zn(OAc)_2$, full conversion was obtained in 24 h at 60°C (Table 2, Entry 1-2). α-Amino esters and derivatives are typically sold as their HCl salts and require liberation of the free amine prior to the transamidation. *In situ* amine release from these salts is therefore desirable. Interestingly, a combination of **L-5a.HCl** with DIPEA showed to have no effect on the conversion (Table 2, Entry 3; Table S3). As a base was not required in our esterification protocol[20] a selection of catalysts, featuring various $M^{II}OAc_2$ (Zn, Co, Ni, Cu) and ZnX_2 salts (OAc, Acac, formate, OTf, Cl) that performed well in the alcoholysis was tested with DIPEA as base (Table S5). Interestingly, Zn formate.$2H_2O$, $Cu(OAc)_2$ and $Ni(OAc)_2$ performed well, although less efficient than $Zn(OAc)_2$. $ZnCl_2$ performed significantly worse than $Zn(OAc)_2$ which supports the hypothesis that the acetate ligand contributes to the reaction's efficiency by activation of the nucleophile with hydrogen bonding, in accordance with the computed alcoholysis mechanism (Scheme 1b).[20] The best catalysts were then cross-checked with different tertiary amines as bases (Table 2, Entry 4-5; Table S6). This revealed $Zn(OAc)_2/Et_3N$ as an optimal catalyst/base system, giving full conversion at 50°C (Table 2, Entry 5). The excess of amino acid ester could be reduced

to 1.1 equivalents providing a higher temperature (70°C) and catalyst loading (20 mol%) were used (Table 2, Entry 6-8). Considering $Zn(OAc)_2$ is cheap and an authorized food additive (E650) a lower loading of nucleophile **L-5a.HCl** is more interesting.

Safeguarding amino acid stereochemistry is crucial in peptide synthesis. The effect of the transamidation on the chirality of both the *t*Bu nic amide and amino acid ester hydrochloride was therefore evaluated. Under the optimized reaction conditions, the chirality was jeopardized, showing a mixture of **L,L-6a** and **D,L-6a** in an 88:12 ratio (Table 2, Entry 8; Scheme S1). This led us to further investigate the effect of base on the reaction (Table S10). Gratifyingly, NaOAc turned out to allow full conversion without epimerization (Table 2, Entry 9).

Table 2. Selected optimization steps of the transamidation with model system **L-4a** and **L-5a.HCl**.[a]



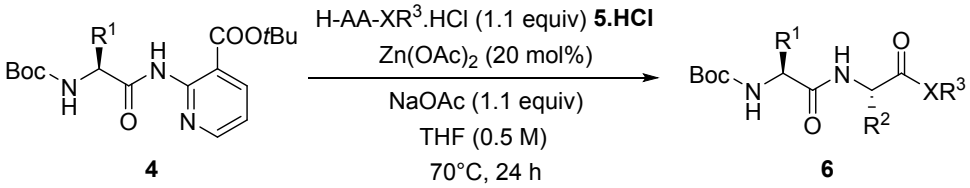
Entry	Amine Form (*X* equiv)	Base[b]	$Zn(OAc)_2$ (*Z* mol%)	T [°C]	Yield **L-4a** [%]	Yield **6a** [%]
1	**L-5a** (3 equiv)	-	10	40	23	77
2	**L-5a** (3 equiv)	-	10	60	0	quant.
3	**L-5a.HCl**	DIPEA	10	60	0	quant.

	(3 equiv)					
4	**L-5a.HCl** (3 equiv)	DIPEA	10	50	17	83
5	**L-5a.HCl** (3 equiv)	Et_3N	10	50	0	quant.
6	**L-5a.HCl** (1.1 equiv)	Et_3N	10	50	25	75
7	**L-5a.HCl** (1.1 equiv)	Et_3N	10	70	14	86
8	**L-5a.HCl** (1.1 equiv)	Et_3N	20	70	0	quant. (67[c])
9	**L-5a.HCl** (1.1 equiv)	NaOAc	20	70	0	quant. (79[d])

[a] Reaction conditions: Boc-L-Phe-*t*Bu nic (**L-4a**) (0.25 mmol), H-L-Phe-OMe.HCl (**L-5a)** or **L-5a.HCl** (*X* equiv), base (*Y* equiv), $Zn(OAc)_2$ (*Z* mol%), THF (0.5 ml). ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. Isolated yield between brackets. [b] equiv of base in a 1:1 ratio to amine. [c] HPLC with *n*-hexane:ethanol (65:35) on a Diacel Chiralpak IA column shows a mixture of **L,L:D,L-6a** (88:12). [d] HPLC with *n*-hexane:ethanol (65:35) on a Diacel Chiralpak IA column shows only **L,L-6a**.

With these optimized conditions in hand (Table 2, Entry 9), we set out to examine the scope of the transamidation reaction through the synthesis of different dipeptides (Table 3). Amino acid amides and esters featuring side chains with different sterical hindrance and functional groups, both at the level of the substrate and nucleophile, were used successfully (Table 3). Transamidation of the challenging proline amide **L-4d** (Table 3, Entry 4) as well as a reaction with H-L-Trp-OBn.HCl (**L-5e.HCl**) nucleophile (Table 3, Entry 5), possessing an unprotected indole in the side chain, were tolerated. When using amino acid amides as the nucleophile, featuring a primary amide, full conversion could be obtained by prolonging the reaction time to 48 h (Table 3, Entry 6) or by using 3 equiv nucleophile (Table 3, entry 7 and 8). The latter conditions were also suitable to perform reactions with rarely used and epimerization sensitive amino acid amides. Boc-L-Cys(*t*Bu)-NH-*t*Bu nic (**L-4l**) and Boc-L-His(trt)-NH-*t*Bu nic (**L-4m**) smoothly reacted with H-L-Lys(Cbz)-OMe.HCl (**L-5h.HCl**) giving 57% and 72% yield (Table 3, entry 10 and 11). Challenging H-L-Pro-OMe.HCl (**L-5g.HCl**) involving a secondary amine resulted in only 50% conversion in 24 h with 3 equiv nucleophile. An additional increase in temperature to 100°C was required to obtain full conversion in 24 h (Table 3, Entry 9). The substrate can also be a peptide as exemplified by coupling of **L,L-4l** with H-L-Phe-OMe.HCl (**L-5a.HCl**) giving the tetramer **L,L,L-6k** in 88% isolated yield (Table 3, Entry 12). Interestingly, in all the transamidations of Table 3 no sign of epimerization was observed as judged by HPLC and NMR analysis.

Table 3. Scope of the transamidation reaction for the synthesis of various dipeptides **6** from **L-4** and **L-5.HCl**.[a]



Entry	Boc-AA-NH-*t*Bu nic **4**	Amine **5.HCl**	**6**	Yield [%][b]
1	Boc-L-Phe-NH-*t*Bu nic **L-4a**	H-L-Phe-OMe.HCl **L-5a.HCl**	**L,L-6a**	95
2	Boc-L-Ala-NH- *t*Bu nic **L-4b**	H-L-Leu-OAll.HCl **L-5b.HCl**	**L,L-6b**	99
3	Boc-L-Tyr(*t*Bu)-NH-*t*Bu nic **L-4c**	H-L-Val-O*t*Bu.HCl **L-5c.HCl**	**L,L-6c**	85
4	Boc-L-Pro-NH-*t*Bu nic **L-4d**	H-L-Leu-OMe.HCl **L-5d.HCl**	**L,L-6d**	95
5	Boc-L-Met-NH-*t*Bu nic **L-4e**	H-L-Trp-OBn.HCl **L-5e.HCl**	**L,L-6e**	80
6	Boc-βAla-NH-*t*Bu nic **4f**	H-L-Phe-NH_2.HCl **L-5f.HCl**	**L,L-6f**	72[c]
7	Boc-βAla-NH-*t*Bu nic **4f**	H-L-Phe-NH_2.HCl **L-5f.HCl**	**L,L-6f**	74[d]
8	Boc-L-Met-NH-*t*Bu nic **L-4e**	H-L-Phe-NH_2.HCl **L-5f.HCl**	**L,L-6g**	89[d]

9	Boc-L-Ala-NH- *t*Bu nic **L-4b**	H-L-Pro-OMe.HCl **L-5g.HCl**	**L,L-6h**	68[d,e]
10	Boc-L-Cys(*t*Bu)-NH-*t*Bu nic **L-4l**	H-L-Lys(Cbz)-OMe.HCl **L-5h.HCl**	**L,L-6i**	57%[d]
11	Boc-L-His(trt)-NH-*t*Bu nic **L-4m**	H-L-Lys(Cbz)-OMe.HCl **L-5h.HCl**	**L,L-6j**	72%[d]
12	Boc-L-Pro-L-Leu-Gly-NH-*t*Bu nic **L,L-4n**	H-L-Phe-OMe.HCl **L-5a.HCl**	**L,L,L-6k**	88

[a] Reaction conditions: Boc-L-AA-*t*Bu nic (**4**), Amine (**L-5a.HCl)** (1.1 equiv), NaOAc (1.1 equiv), $Zn(OAc)_2$ (20 mol%), THF (0.5 M). [b] Isolated yield. [c] 48 h. [d] 3 equiv of the amine and 3 equiv of NaOAc. [e] T = 100°C.

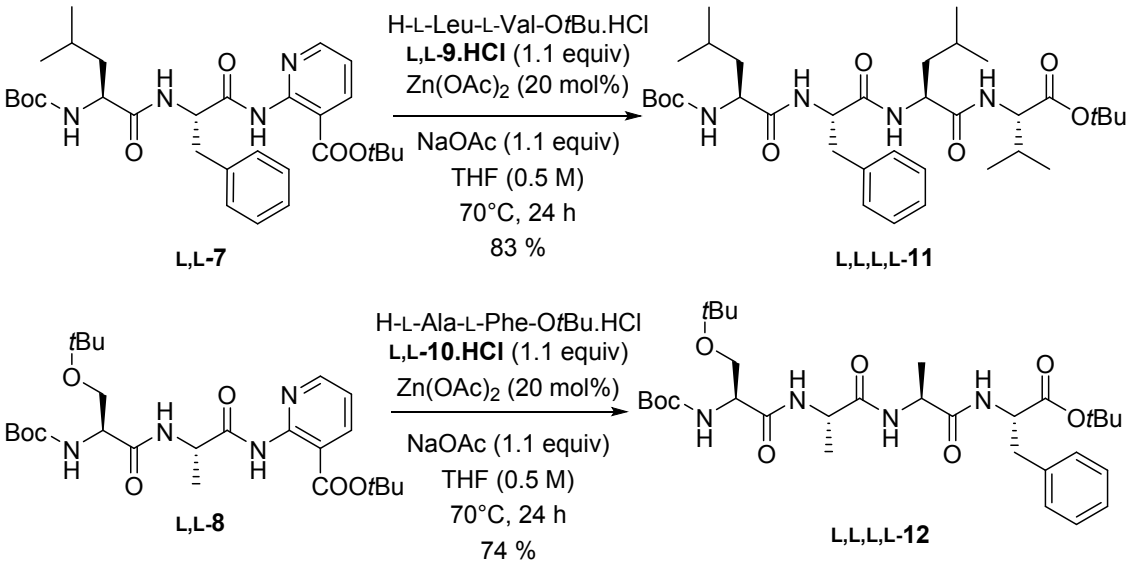
Segment condensation was subsequently studied. *t*Bu nic derivatized dipeptides **L,L-7** and **L,L-8** were assembled from the corresponding *N*-Boc *N'-t*Bu nic amino acid amides, **L-4a** and **L-4b**, respectively with standard coupling/deprotection protocols (e.g. Scheme 2a for the synthesis of **L,L-7**). These dipeptides were engaged in a segment condensation through transamidation with, respectively, H-L-Leu-L-Val-O*t*Bu.HCl (**L,L-9.HCl**) and H-L-Ala-L-Phe-O*t*Bu.HCl (**L,L-10.HCl**) under standard conditions (Scheme 4). Both tetramers **L,L,L,L-11** and **L,L,L,L-12** could be isolated in a good yield, without loss of chiral information (see Supporting Information, Section 5.4).

Importantly, the methodology's compatibility with a solid support was also confirmed. The side chain of Gln of solid phase assembled and resin-bound tetrapeptide Boc-Gln(*t*Bu nic)-Phe-Lys(Boc)-Phe-NH-Rink amide resin (**13**) was coupled with H-Ala-O*t*Bu.HCl (**L-5h.HCl**) (5 equiv) (Scheme 5). By application of 5 equiv NaOAc as base and 20 mol% of $Zn(OAc)_2$ in THF as solvent, full conversion was noted after 48 h reaction time at 90°C. The pentapeptide **14.TFA** was isolated upon TFA/TIS/H_2O cleavage of the resin with a yield of 59% (preparative HPLC). Hereafter, the compatibility of the

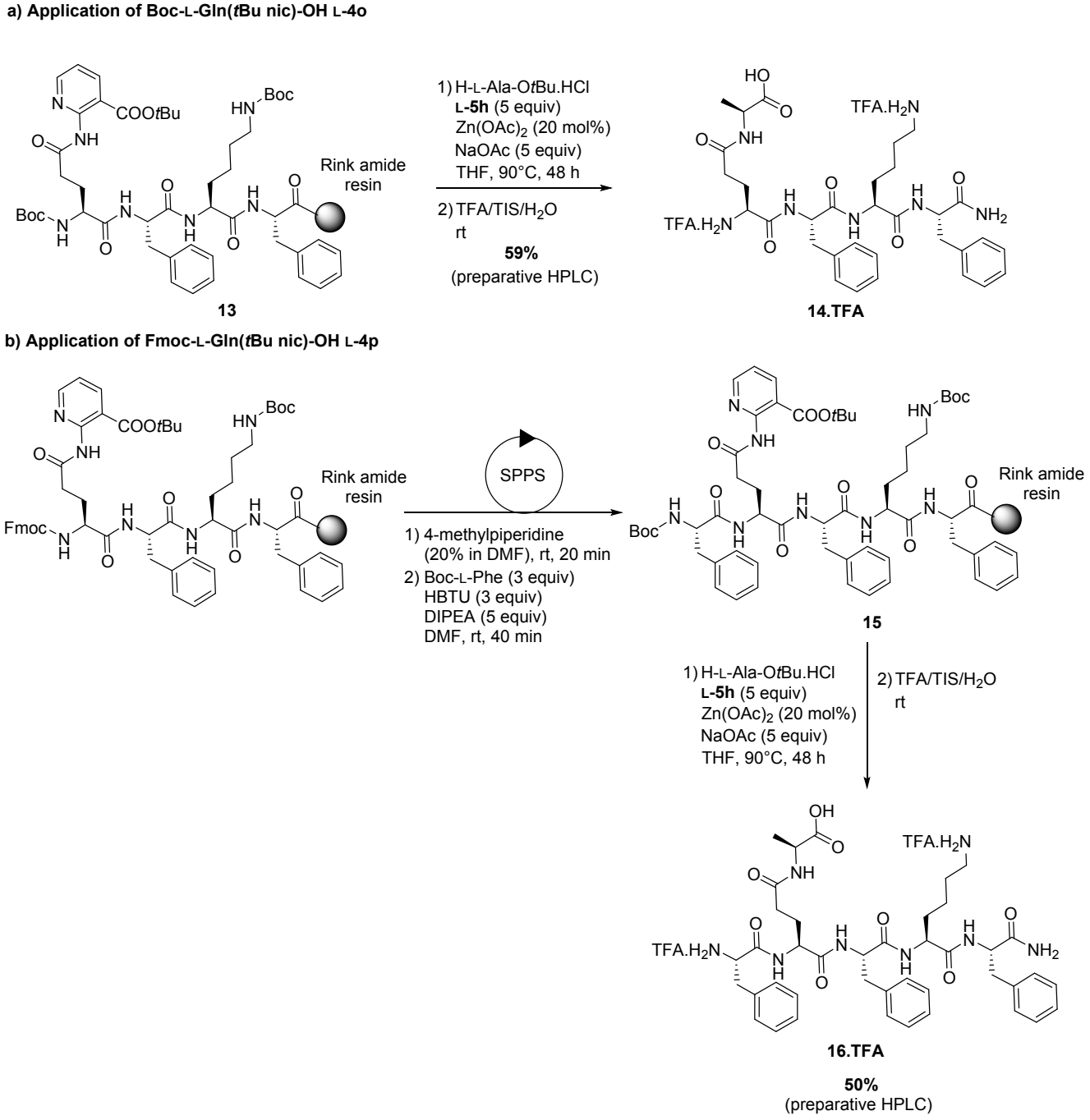
functionalized amide with Fmoc deprotection was established by using Fmoc-L-Gln(*t*Bu nic)-OH (**L-4p**) in the synthesis of Boc-L-Phe-L-Gln(*t*Bu nic)-L-Phe-L-Lys(Boc)-L-Phe-NH-Rink amide resin (**15**) through solid phase synthesis (SPPS). Subsequent amide cleavage was demonstrated under the same conditions as used for **13**, yielding peptide **16.TFA** in 50% yield (Scheme 5). These examples demonstrate that solid supported reactions are within reach and chemoselective side chain derivatization, through use of the Boc-(**L-4o**) and Fmoc-Gln(*t*Bu nic)-OH (**L-4p**) building blocks, fully orthogonal to classical peptide synthesis is possible.

Macrocyclization *via* our transamidation was demonstrated by the synthesis of an allylated analog of Stylissatin A. This cyclic heptapeptide natural product, first isolated from the Papua New Guinean marine sponge, *Stylissa massa*, was reported to possess inhibitory activity on nitric oxide production.[24] Cyclization of linear precursor *t*Bu nic equipped peptide **17.HCl** was smoothly achieved at 100°C. Full conversion was obtained within 24 h and the cyclic 7-mer **18** was isolated by means of preparative HPLC purification (Scheme 6). To the best of our knowledge this is the first cyclic peptide synthesis based on a transamidation.

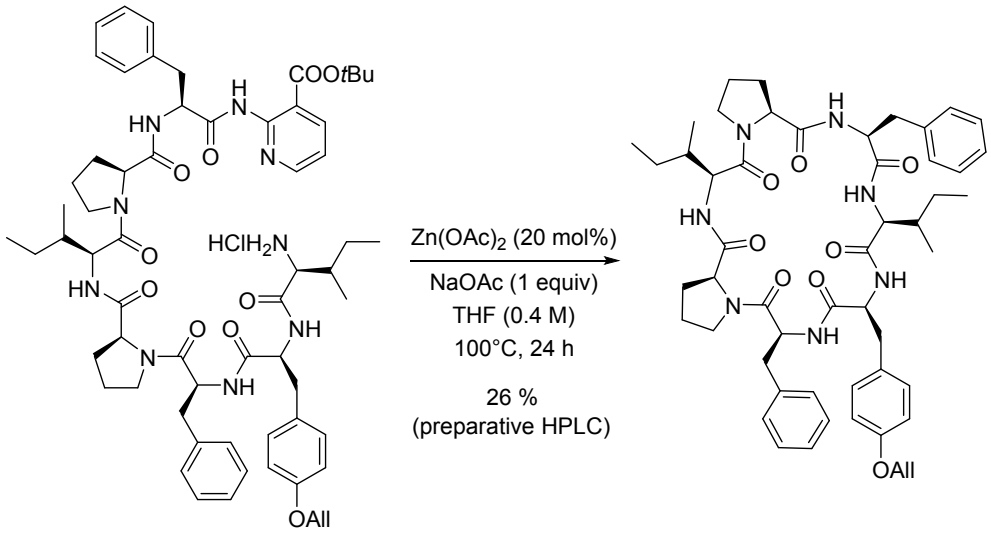
Scheme 4. Application of the methodology through dipeptide segment condensations.



Scheme 5. Application of the methodology through solid-phase side chain derivatization of peptide **13** and **15** involving Boc-Gln(*t*Bu nic)-OH (**L-4o**) (a) and Fmoc-Gln(*t*Bu nic)-OH (**L-4p**) (b) building blocks



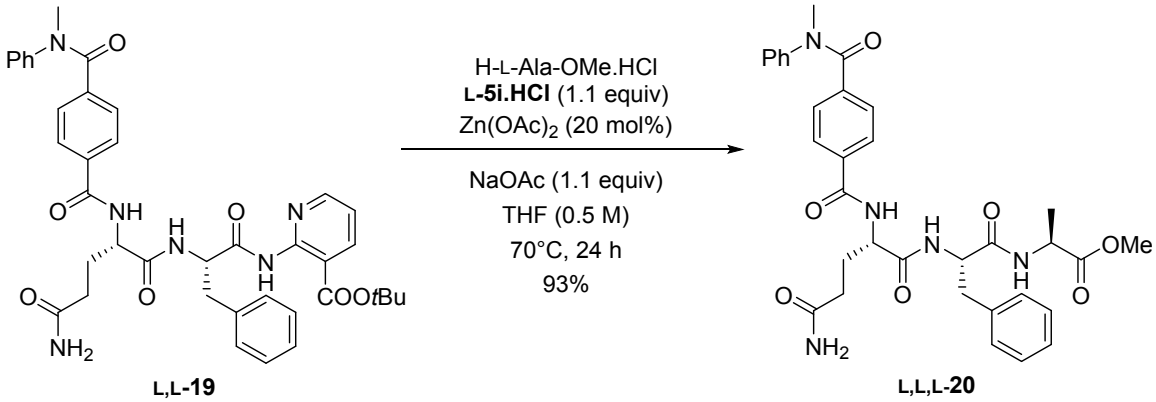
Scheme 6. Application of the methodology through macrocyclization of heptapetide **17.HCl**



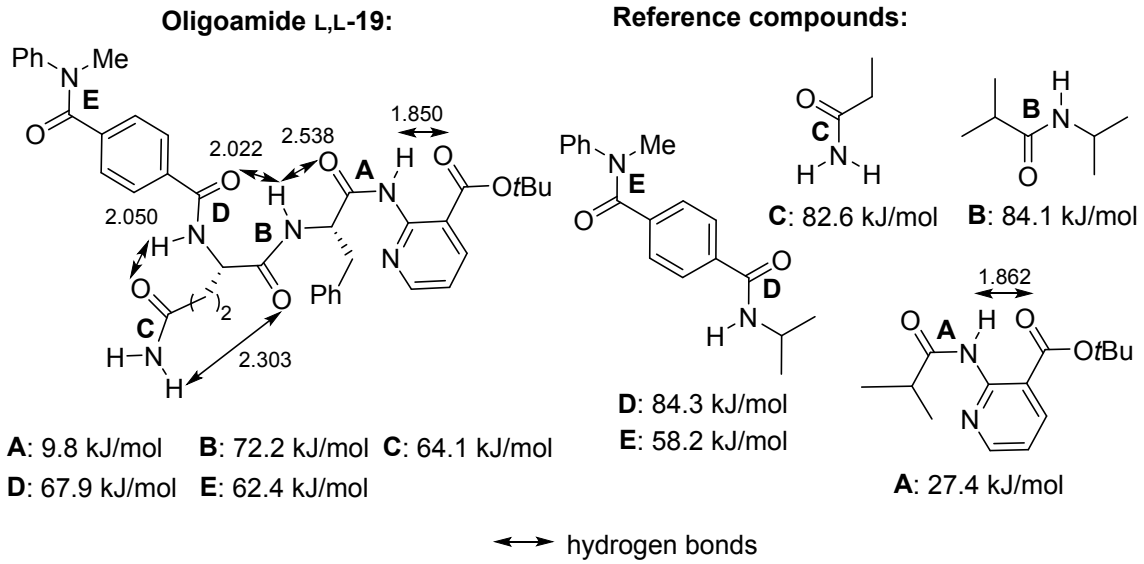
17.HCl **18**

To further demonstrate the chemoselectivity of our transamidation, we selected **L,L-19**, a substrate containing five electronically and sterically different amides (primary, secondary and tertiary amides derived from aromatic and aliphatic carboxylic acids, both *N*-alkyl and *N*-aryl variants) (Scheme 7). Reaction of **L,L-19** with H-L-Ala-OMe.HCl (**L-5i.HCl**) as the nucleophilic partner resulted in full conversion and an excellent 93% yield. No other amides, even the aromatic, beside the acyl-L-Phe-NH-*t*Bu nic one cleaved under these reaction conditions. Also, tertiary *N*-methyl-*N*-phenylbenzamide, which is known to be activated under Ni-catalysis,[13a] does not cleave. In fact, an aliphatic amide selectively transamidates in the presence of aromatic amides. Calculations of the resonance energies of the 5 amides supported the L-Phe-NH-*t*Bu nic moiety to be the most reactive in transamidation (Scheme 8).[25] Interestingly, conformational analysis in **L,L-19** revealed several intramolecular interactions, responsible for the lowering of the resonance energies in comparison with simple model reference amides.

Scheme 7. Application of the methodology on an peptide derived oligoamide **L,L-19**



Scheme 8. Calculated resonance energies of the amides in **L,L-19** and reference amide compounds



CONCLUSIONS

In summary, we have developed a novel transamidation reaction based on *N*-Boc amino acid amides equipped with a nicotinate DG **4**. The DG can be easily introduced on *N*-Boc amino acid amides under mild conditions *via* Pd-catalyzed amidation with commercially available *t*Bu 2-chloronicotinate (**2**). Synthesis of dipeptides *via* transamidation showed that a wide range of *t*Bu nic-bearing *N*-Boc-protected

amino amides **4** were compatible with both amino acid esters and amides **5** as nucleophiles. **4** can be used as building block under classical peptide coupling conditions, easily allowing complex and challenging peptide/peptidomimetic substrate synthesis for subsequent transamidation, as illustrated by successful segment condensations, a reaction on a solid support and a macrocyclization. The protocol is fully chemoselective for *t*Bu nic bearing amides leaving even the more reactive amides untouched. The use of a cheap and non-toxic Zn catalyst, used as a food additive, renders this mild transamidation fit for the chemical modification of biomolecules.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed optimization data, experimental procedures, characterization data, and copies of NMR spectra of all compounds (PDF).

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DEDICATION

In memory of Professor Benjamin Van der Veken (1947–2019)

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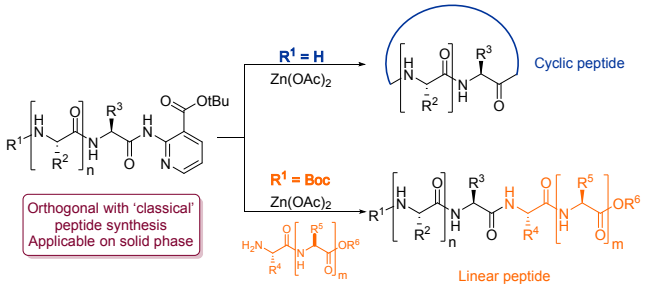
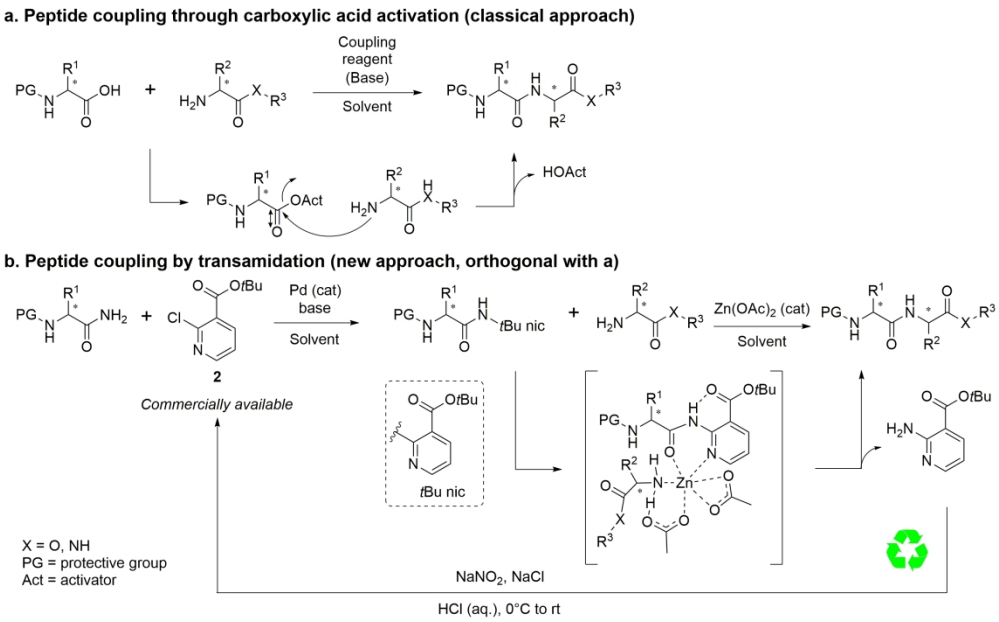
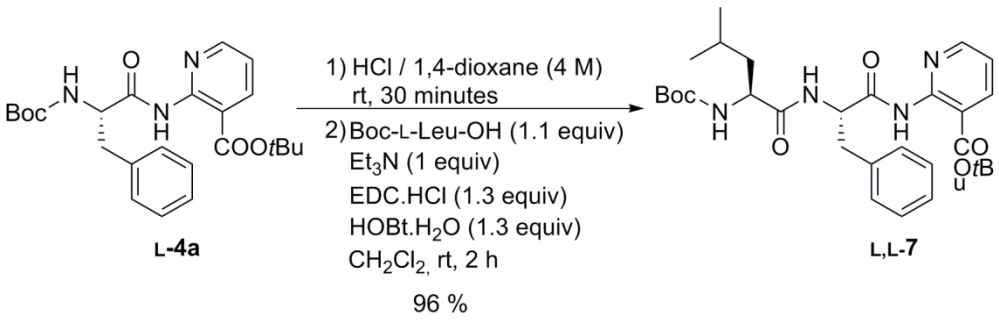
Graphical abstract





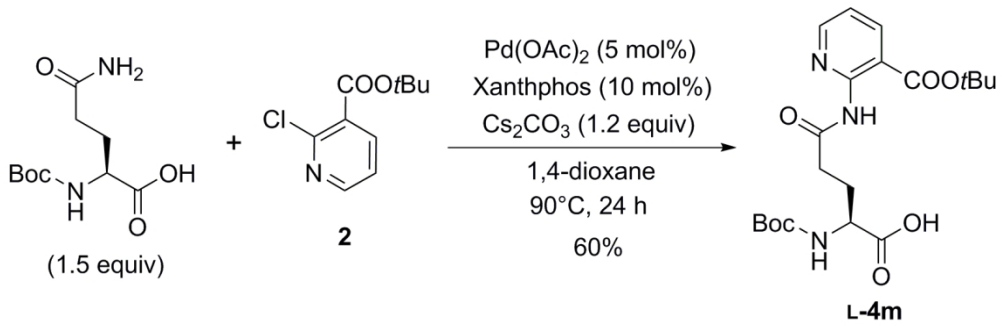
Peptide synthesis: (a) Traditional approach: carboxylic acid activation and (b) New approach: Zn-catalyzed nicotinate-directed transamidation.

237x146mm (300 x 300 DPI)



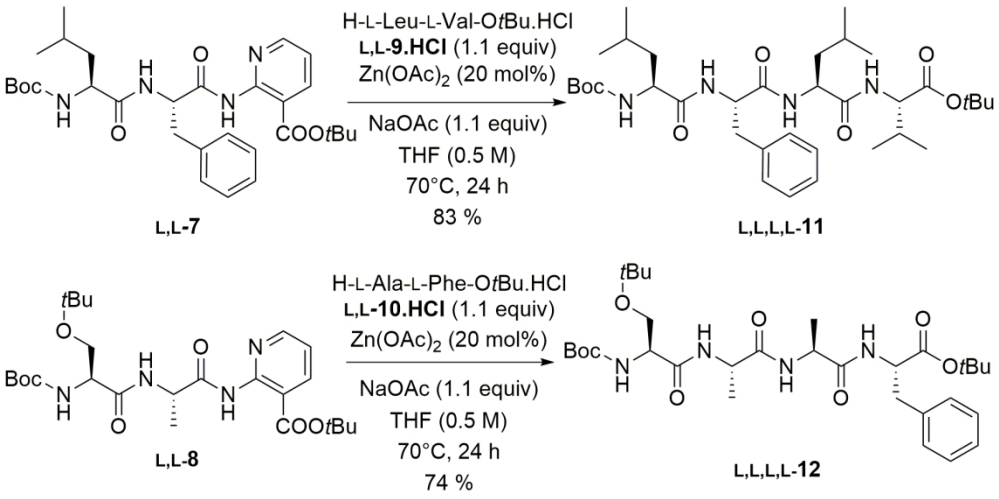
Synthesis of tBu nic-functionalized dipeptide L,L-7 via application of Boc-L-Phe-tBu nic L-4a in classical peptide synthesis (a) and Pd-catalyzed amidation of Boc-L-Leu-L-Phe-NH2 with tBu NicCl (2) (b).

145x46mm (300 x 300 DPI)



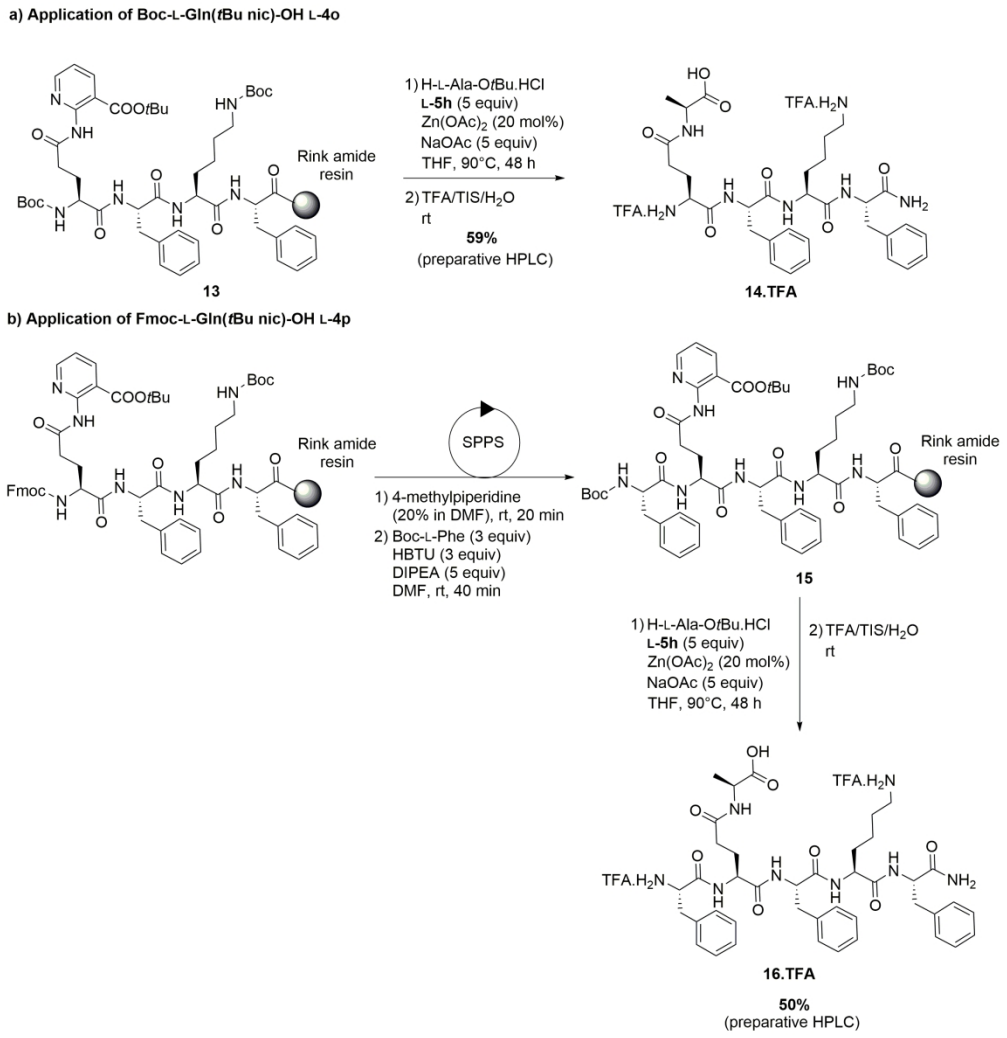
Synthesis of Boc-L-Gln(NH-tBu nic)-OH (L-4o) via Pd-catalyzed amidation of Boc-L-Gln-OH with tBu NicCl (2).

142x46mm (300 x 300 DPI)



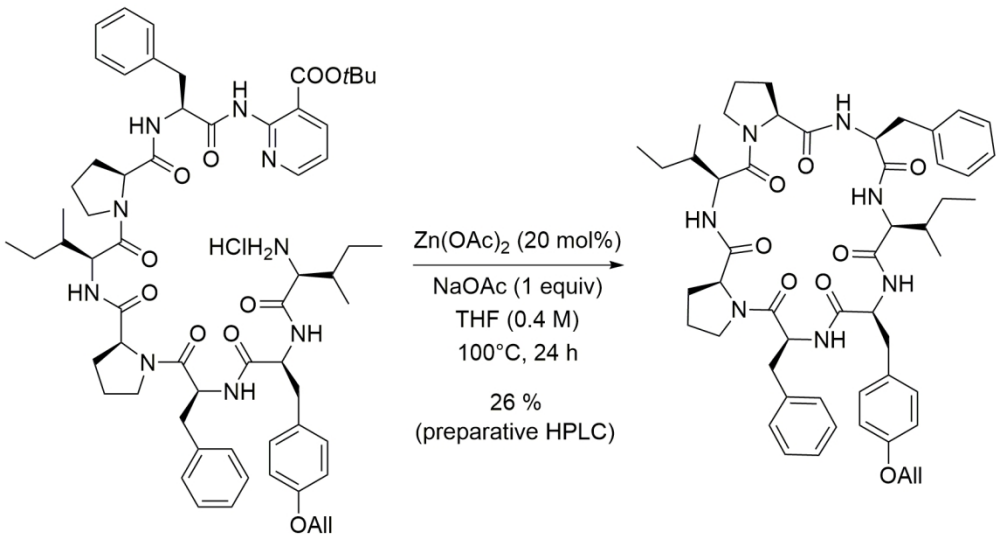
Application of the methodology through dipeptide segment condensations.

160x79mm (300 x 300 DPI)



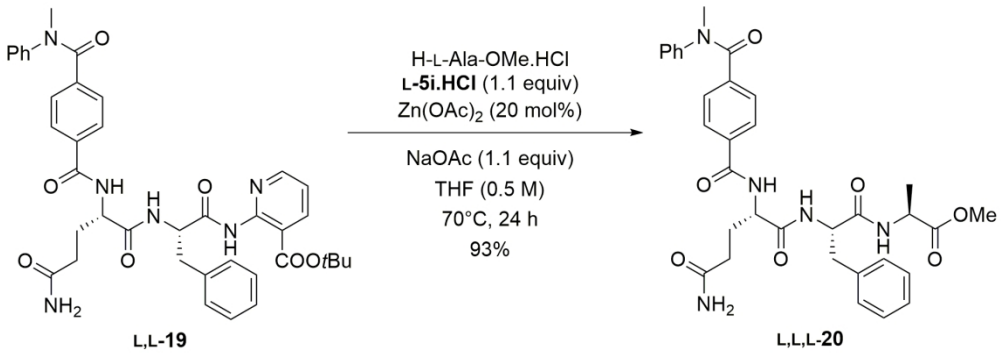
Application of the methodology through solid-phase side chain derivatization of peptide 13 and 15 involving Boc-Gln(tBu nic)-OH (L-4o) (a) and Fmoc-Gln(tBu nic)-OH (L-4p) (b) building blocks

224x231mm (300 x 300 DPI)



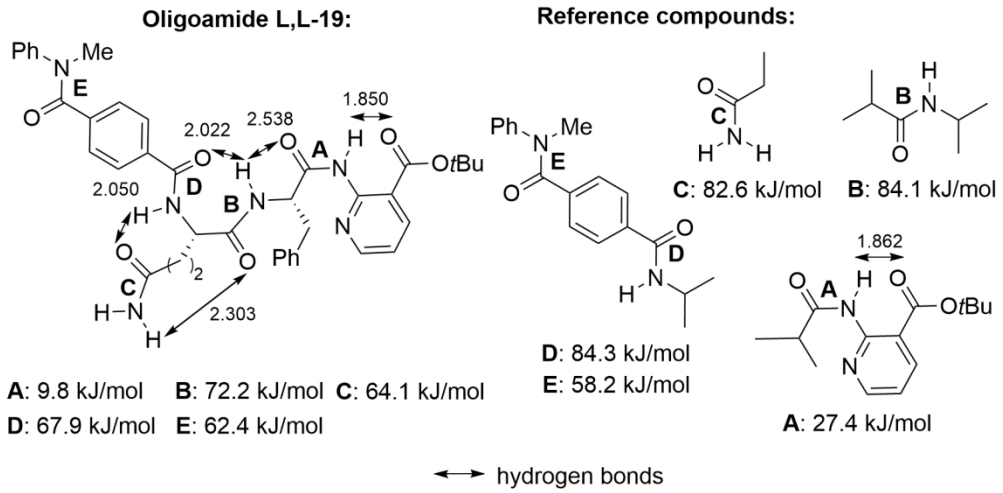
Application of the methodology through macrocyclization of heptapetide 17.HCl

151x87mm (300 x 300 DPI)



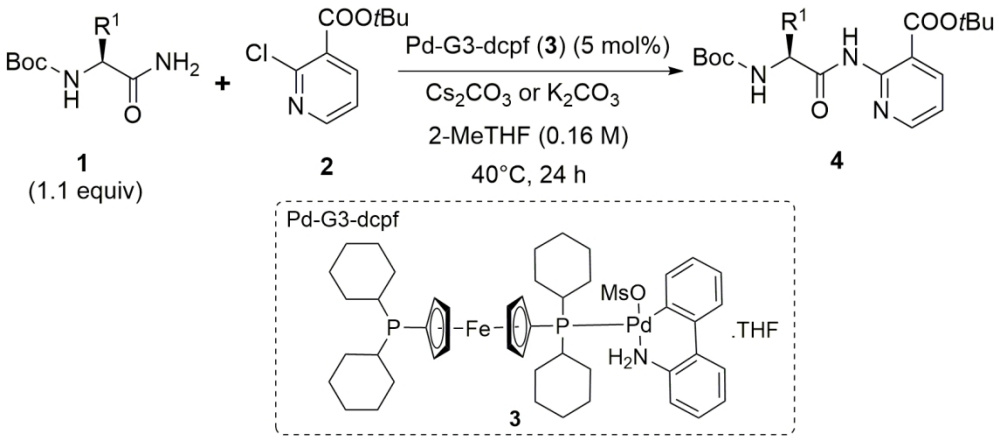
Application of the methodology on an peptide derived oligoamide L,L-19

170x60mm (300 x 300 DPI)



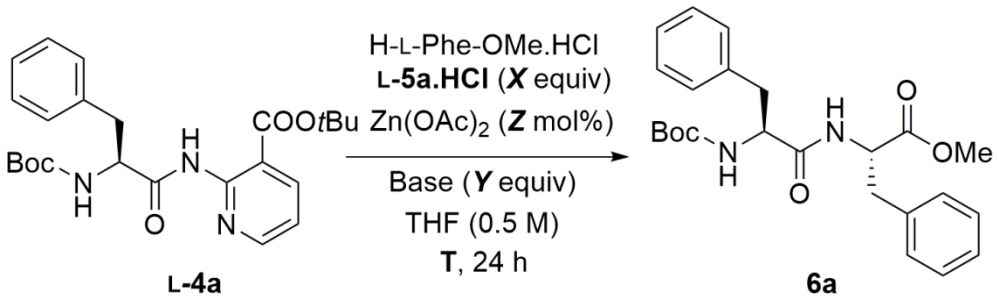
Calculated resonance energies of the amides in L,L-19 and reference amide compounds

151x75mm (300 x 300 DPI)



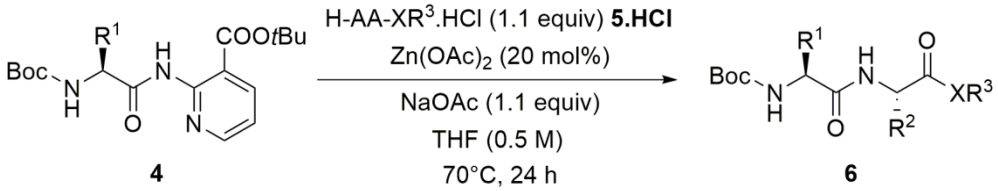
Synthesis of N-Boc N□-tBu nic amino acid amides (4) via Pd-catalyzed amidation of N-Boc amino acid / peptidic amides (1) with tBu NicCl (2).

143x63mm (300 x 300 DPI)



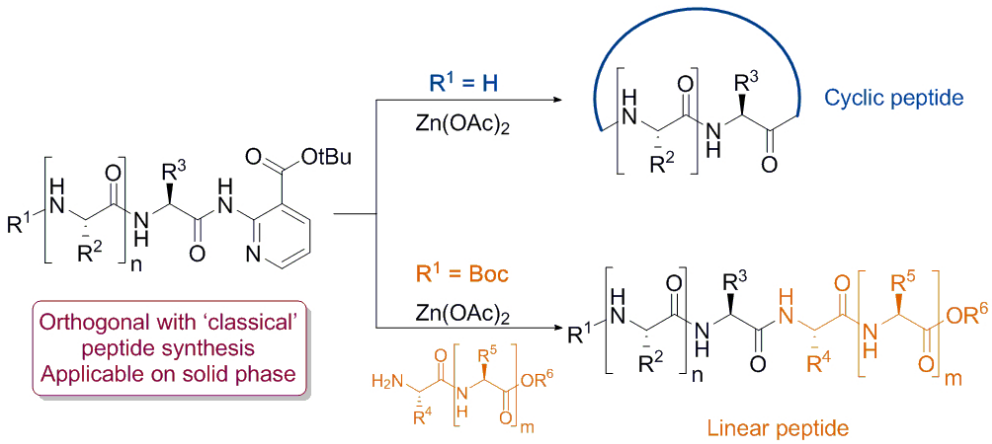
Selected optimization steps of the transamidation with model system L-4a and L-5a.HCl.[a]

123x37mm (300 x 300 DPI)



Scope of the transamidation reaction for the synthesis of various dipeptides 6 from L-4 and L-5.HCl.[a]

144x29mm (300 x 300 DPI)



85x38mm (300 x 300 DPI)