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Directed C–H Functionalization Reactions with a Picolinamide Directing Group: Ni-Catalyzed Cleavage and By-Product Recycling

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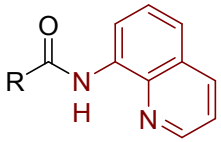
ABSTRACT: An efficient strategy for the cleavage of the picolinamide directing group (DG) and recycling of the by-product generated has been developed. In this protocol, picolinamides were first Boc activated into tertiary *N*-Boc-*N*-substituted picolinamides. These were then cleaved via a Ni-catalyzed esterification reaction with EtOH to give valuable *N*-Boc protected amines. $Ni(cod)_2$ was used as a catalyst without any ligands or base additives. The by-product, ethyl 2-picolinate can be used to install the picolinamide DG in a direct or indirect manner on amines. The protocol exhibits a broad functional group tolerance and high yields. To demonstrate the utility of this approach, it was applied on a number of selected examples from the recent C−H functionalization literature featuring 2-picolinamide as a DG.

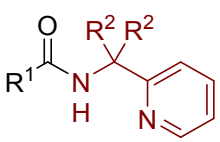
Introduction

The use of a directing group (DG) in transition metal (TM)-catalyzed C–H bond functionalization reactions provides a versatile approach for the efficient selective (regio, stereo) and step economical synthesis of organic materials, agrochemicals, pharmaceuticals and complex natural products.[1,2] Various amide based mono- and bidentate DGs have been developed which are derived from either carboxylic acid or amine substrates (Figure 1).[3–6] Among those *N*,*N*-bidentate directing groups, picolinamide (PA), introduced by Daugulis,[3] has widely been used for regioselective C–H bond functionalization of amines (alkylation,[7] alkenylation,[8] alkynylation,[9] arylation,[10] amination/amidation,[11] acyloxylation,[12] borylation,[13] cyanation,[14] trifluoromethylation,[15] and sulfonylation[16] reactions). The picolinoyl moiety can be easily introduced on an amine substrate by reaction with 2-picolinic acid in the presence of an activator (HATU, TBTU, EDCI, HOBt, $EtCO_2Cl$).[7d,10d,11a,12a,16,17] After C–H bond functionalization, the PA auxiliary needs to be removed to unlock the free amine functionality as the DG is usually not a desired functionality in the reaction product. Unfortunately, the cleavage of this secondary amide is difficult due to the inherent stability of the amide due to the conjugation between the carbonyl group and the nitrogen atom.[18]

A) RCOOH derived:

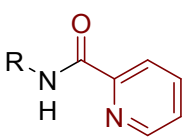


Daugulis (2005)

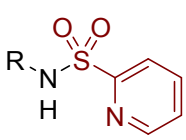


R^2 = H: Chatani (2011)
R^2 = Me: Shi (2013)

B) RNH_2 derived:



Daugulis (2005)



Carretero (2011)
Fernández Ibáñez

Figure 1. Common *N*,*N*-bidentate (sulfon)amide based DGs for transition metal-catalyzed C–H bond functionalization: Carboxylic acid derived (A) and amine derived (B).

Over the past few years, several approaches have been developed for the removal of the PA auxiliary. Known methodologies for the cleavage of this DG are shown in Figure 2A. Some of these strategies have, besides on secondary, also been used for tertiary picolinamides. The most common approach is the hydrolysis under basic condition (e.g. using NaOH in EtOH at 70 °C).[7a,10b,10g,11b–f,19] Chen's group introduced a modified picolinamide where a silylated hydroxymethyl group is attached at the ortho position of the PA to facilitate its removal under acidic condition. When the modified PA was treated with aq. HCl in MeOH at 80 °C, a furo[3,4-*b*]pyridin-7(5*H*)-one is obtained upon amide cleavage allowing to recycle the auxiliary in moderate yield.[7b,10a,10c] A number of examples are reported using acidic hydrolysis lacking this ortho substituent.[7d,15,20] However, then harsh conditions are required and therefore often lead to functional group incompatibilities. The group of You and co-workers reported the deprotection of the picolinamide group by treatment with boron trifluoride-diethyl etherate ($BF_3 \cdot Et_2O$), but the harsh Lewis acidic nature of BF_3 also limited its application.[21] Other Lewis acid catalysts such as $AlCl_3$ were used as well.[9] A reductive acidic cleavage (Zn, HCl) was disclosed by Maulide,[10h] Carretero,[8b] and Spring[22] but only limitedly studied. Daugulis treated a tertiary picolinoylamide with $LiEt_3BH$ for PA removal.[11a] In one example, Shi's group used PCl_5/2,4-lutidine in the presence of MeOH to obtain the corresponding imino ether via the formation of imidoyl chloride intermediate, and subsequent aqueous work-up resulted in the free amine.[23] Unfortunately, all these methods have their own limitations with respect to functional group compatibility and can't be applied as a general approach for the cleavage of the PA moiety. Moreover, not all approaches allow (easy) recycling of the picoline by-product derivative. Clearly a new mild (neutral conditions) and generally applicable method would be desirable.

In 2015 Garg reported the first oxidative addition of the C–N bond of an activated tertiary amide to a transition metal complex.[24,25a] A $Ni(cod)_2$/SIPr precatalytic system was applied for the esterification of *N*-methyl-*N*-phenylarenecarboxamides. Subsequently, in 2016 the same group disclosed that tertiary *N*-alkyl-*N*-Boc-alkanecarboxamides could also be used when using $Ni(cod)_2$/terpyridine.[25b] This extended the applicability significantly as both secondary *N*-alkylalkane- and *N*-alkylarenecarboxamides can be activated for TM catalysis by simple Bocylation.

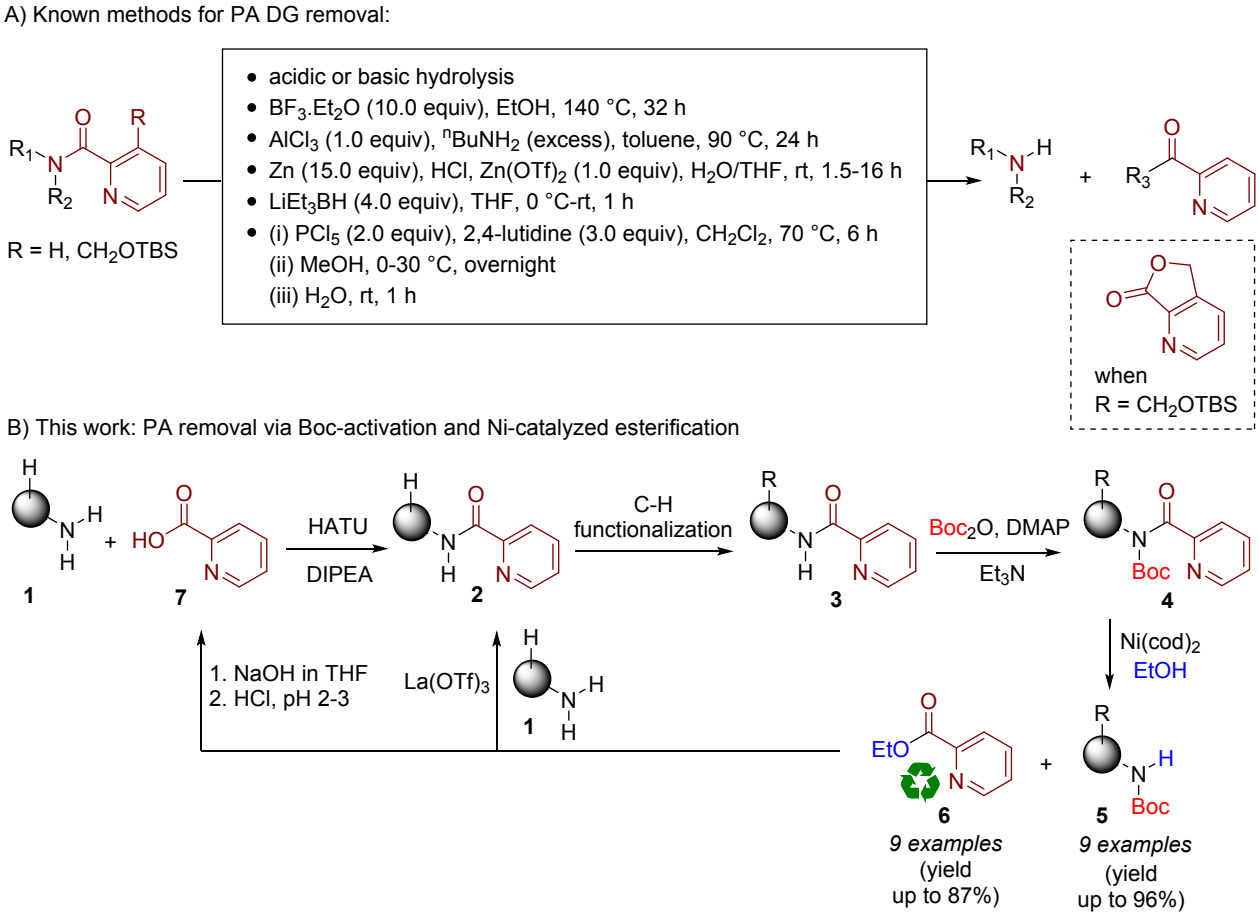


Figure 2. Known picolinamide (PA) cleavage methods (A) and our approach (B).

We wondered whether such an approach could be used to cleave the picolinamide directing group (Figure 2B). Secondary PA featuring a N–H (**2**/**3**) does not undergo C–N bond cleavage with transition metal catalysts when unactivated and is therefore expected to be fully orthogonal with the C–H functionalization reaction. After C–H functionalization, PA can be activated by a simple Bocylation and subsequently be removed as ethyl 2-picolinate by a Ni-catalyzed esterification reaction on tertiary *N*-Boc-*N*-substituted picolinamides (**4**) using EtOH. Ni-catalyzed reactions on tertiary *N*-Boc-*N*-substituted amides are typically performed aiming to obtain carboxylic acid derivatives and not *N*-Boc protected amines like in our case. Boc deprotection into target amines can be easily obtained with strong acid or under thermal treatment.[26a-b] In addition, the carbamate can also be directly transformed into another functional group.[26c-f] The by-product, ethyl 2-picolinate (**6**) can be directly used as a precursor for DG installation by amidation under Lewis acid catalysis. Alternatively, hydrolysis to picolinic acid (**7**) which is then coupled with amine substrate making use of a (super)stoichiometric coupling agent can be opted.[17]

Ni-catalyzed esterification has only been used to cleave unactivated *N*-quinolin-8-yl amides by employing $Ni^{II}(tmhd)_2$, interestingly acting both as Lewis acid and Bronsted base, in methanol or in a one-pot process with follow-up transesterification of crude methyl ester with another alcohol

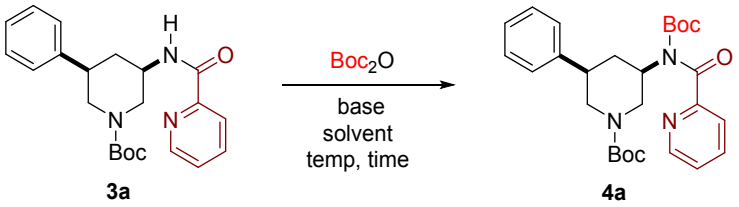
using a [(salen)Fe^{III}]$_2$O catalyst when other esters are required.[27] Activated *N*-quinolin-8-yl-*N*-Boc tertiary amides have been used in transamidations providing immediate access to a variety of *N*-substituted amides and do not require Ni catalysis.[28] Ni-catalyzed esterification on *N*-alkyl/aryl-*N*-Boc picolinamides have to the best of our knowledge not been reported. Transamidations on these substrates are not interesting when aiming by-product recycling. After all, though they can release product amine, the picolinamide by-product generated will be very unreactive to use as a reactant to install the PA DG, either directly via transamidation or indirectly via amide hydrolysis.

Results and Discussion

In our previous work on diastereoselective remote directed C(sp^3)–H arylation of 3-aminopiperidines we have used a picolinamide as DG and demonstrated a basic hydrolysis (NaOH, *i*PrOH, 82 °C) for the cleavage of the picolinamide in the *tert*-butyl *cis*-3-[pyridine-2-carbonyl)amino]-5-arylpiperidine-1-carboxylate reaction products (**3a**).[10d] Though chemoselective amide hydrolysis versus the carbamate protective group was obtained, these reaction conditions are not compatible with a variety of functional groups present in the aryl group. The feasibility of the proposed alternative two-step *N*-Bocylation and Ni-catalyzed esterification protocol was therefore evaluated on model substrate **3a**. Accordingly, we commenced this work by optimizing the Boc activation reaction (Table 1). Our first attempt of Boc introduction on the picolinoylamide nitrogen of **3a**, following classical reaction conditions using Boc_2O (1.5 eq.) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in acetonitrile at room temperature, was not successful (Table 1 entry 1).[29] We noticed that the substrate was not dissolved completely in acetonitrile and the solution remained turbid even after 24 h of stirring leading to almost no reaction. Changing the solvent to DCM resolved the solubility problem, but unfortunately did not improve the overall yield (Table 1 entry 2). Interestingly, even when the reaction was performed at reflux, the desired product **4a** was only obtained in 7% yield (Table 1 entry 3). Use of other solvents such as dimethyl carbonate (DMC) and *tert*-butanol did not deliver any desired product (Table 1 entries 4–5). Use of an additional base (Et_3N) and excess of Boc_2O (4.0–9.0 equiv) was not successful either (Table 1 entry 6–7).[30] Eventually, using 9.0 equivalent of Boc_2O, 1.1 equivalent Et_3N and 0.2 eq. of DMAP at 50 °C in THF successfully yielded the desired product **4a** in 96% yield (Table 1 entry 8, Table 2 entry 1). Next, we applied the Ni-catalyzed esterification reaction developed by Garg's group [$Ni(cod)_2$ (10 mol%), SIPr (10 mol%) and ethanol (2.0 equiv) in toluene at 80 °C][25a] on our model substrate **4a**. To our satisfaction, the reaction gave quantitative conversion of **4a** to *tert*-butyl *cis*-3-[(*tert*-butoxycarbonyl)amino]-5-phenylpiperidine-1-carboxylate (**5a**) (Table S1 entry 1). Surprisingly, when the reaction was performed without SIPr, also full conversion of **4a** was obtained to give **5a** in 90% isolated yield (Table S1 entry 2, Table 2 entry 1). Gratifyingly, the by-product ethyl 2-picolinate (**6**) was obtained in 73% yield. Application of the Co-catalyzed esterification reported by Gosmini and Danoun with stoichiometric Mn as reductant in DMF/Pyridine gave complete conversion of **4a** with ethanol but only 33% isolated yield of **5a**. Moreover only a trace amount of ethyl 2-picolinate (**6**) was isolated

(Scheme S1).[31] Ligandless Ni-catalyzed esterification with ethanol was therefore retained as optimal for DG removal.

Table 1. Optimization of the *N*-Bocylation of Picolinamide 3a[a]



Entry	Base (equiv)	Boc_2O (equiv)	Solvent	Temp. (°C)	Time (h)	Isolated yield **4a** (%)
1	DMAP (0.1)	1.5	CH_3CN	rt	24	trace
2	DMAP (0.2)	2.0	DCM	rt	21	trace
3	DMAP (0.2)	2.0	DCM	40	17	7[b]
4	DMAP (0.2)	2.0	DMC	85	17	no reaction
5	DMAP (0.2)	2.0	*tert*-BuOH	40	17	no reaction
6	DMAP (0.2 eq.) & Et_3N (3.0 eq.)	4.0	DCM	rt	17	trace
7	DMAP (0.2 eq.) & Et_3N (1.1 eq.)	9.0	THF	rt	24	trace
8	**DMAP (0.2 eq.) & Et_3N (1.1 eq.)**	**9.0**	**THF**	**50**	**24**	**96**

[a] Conditions: **3a** (0.2 mmol, 1.0 equiv), Boc_2O, base, solvent (0.2 M), T, t. [b] 66% **3a** was recovered.

We then selected two other *cis*-3-[(pyridine-2-carbonyl)amino]-5-arylpiperidines featuring sensitive functional groups not compatible with the previously used basic hydrolysis (NaOH, *i*PrOH, 82 °C).[10d] Benzyl *cis*-3-[(pyridine-2-carbonyl)amino]-5-[4-(ethoxycarbonyl)phenyl]-piperidine-1-carboxylate (**3b**) and *tert*-butyl *cis*-3-[(pyridine-2-carbonyl)amino]-5-[1-(benzenesulfonyl)-1*H*-indol-3-yl]piperidine-1-carboxylate (**3c**) respectively contain a hydrolysis sensitive ester ($PhCO_2Et$) and sulfonamide [$PhSO_2N_{indole}$]. Gratifyingly, application of the two step protocol delivered 3-[(*tert*-butyloxycarbonyl)amino]-5-arylpiperidines **5b** and **5c** in 92% and 83% overall yield starting from **3b** and **3c** respectively (Table 2, entries 2 and 3). Interestingly to specifically mention is that the use of a Cbz group on the piperidine nitrogen in **3b** provides two orthogonal protecting groups on the primary (Boc) and secondary amino (Cbz) group in the

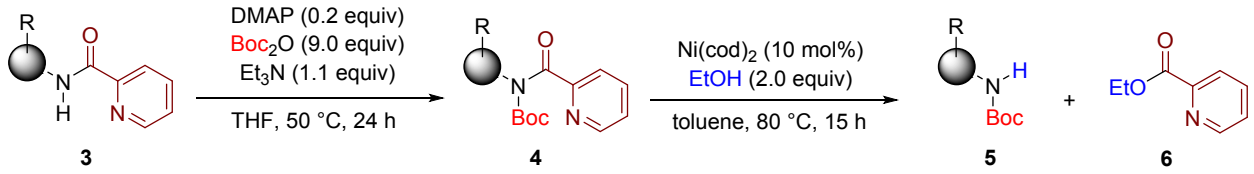
reaction product **5b**, which is very useful for molecular library synthesis.[32] The by-product **6** was also in these cases easily recovered.

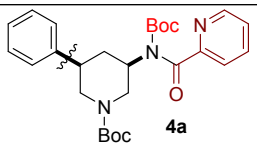
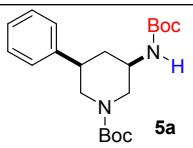
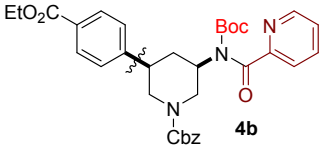
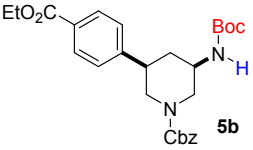
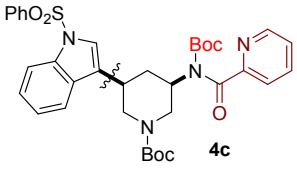
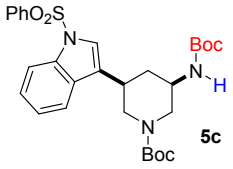
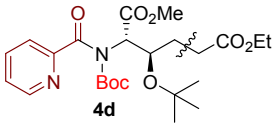
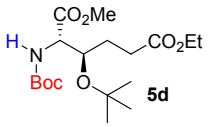
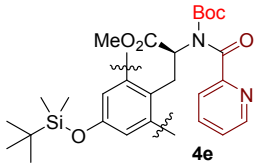
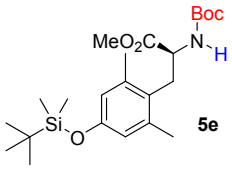
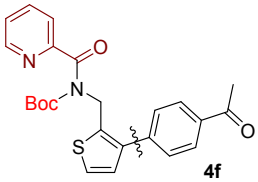
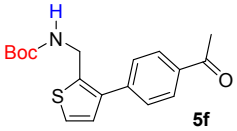
In order to demonstrate the applicability of the protocol, we applied the optimized reaction condition on a variety of other substrates beyond the 3-aminopiperidine core. The picolinamide substrates **3d–i** were synthesized by transition metal-catalyzed C(sp^3/sp^2)–H functionalization reactions from **2** following literature protocols (see Supporting Information for details). These functionalization involved directed arylation[10d–e] (Table 2 entries 1–3, 6), alkylation[7b,7d] (Table 2 entries 4–5), acetoxylation[12a] (Table 2 entry 7), arenesulfonylation[16] (Table 2 entry 8) and amidation[11a] (Table 2 entry 9). These substrates contain aliphatic esters (RCO_2Me, RCO_2Et, BnOAc), ether (O^{t}Bu), silyl ethers (ArOTBS), ketones (ArCOMe), sulphonyl ($PhSO_2Napht$), halogens (chloro), and heteroarene (thiophene) functional groups. These are sensitive to common acidic and/or basic hydrolysis reaction conditions, preventing classical PA cleavage, or pose specific challenges for transition metal catalysis (chloro, benzyl acetate, thiophene). *N*-Bocylation of substrates **3f–h** gave the desired *N*-Boc tertiary amide products **4f–h** with high to near-quantitative yields (86–96%) under standard reaction condition (50 °C, 0.2 equiv DMAP and 1.1 equiv Et_3N) (Table 2 entries 6–8). Both picolinamides derived from aliphatic and aromatic amines could be used. Only the sterically hindered amino acid derivatives (**3d–e**) required a higher reaction temperature (80 °C) and increased amount of Et_3N (3.0–4.0 equiv) and DMAP (0.4 equiv), giving 63% and 96% isolated yields of the desired products **4d** and **4e** respectively (Table 2 entries 4-5). All these activated picolinamide substrates could be esterified with ethanol under the standard esterification conditions [$Ni(cod)_2$ (10 mol%) and ethanol (2.0 equiv), toluene, 80 °C, 15 h]. Substrate **4d** containing CO_2Et, CO_2Me, and a bulky O-^{t}Bu functional group, obtained via directed Pd-catalyzed alkylation of methyl *O*-(*tert*-butyl)-*N*-picolinoyl-L-threoninate (**2d**) with ethyl iodoacetate followed by *N*-Bocylation, gave the corresponding *N*-Boc-amine **5d** in 94% and ethyl picolinate (**6**) in 81% yield (Table 2 entry 4). No epimerization occurred at the α-position of the amino acid derivative **5d** since only one set of peaks were observed in ^1H and ^{13}C NMR (see spectra in the SI). Interestingly, the bis methylated tyrosine derived picolinamide **4e** containing the acid/base labile OTBS functional group was also well tolerated and gave *N*-Boc-amine **5e** in 82% yield and **6** in 72% yield (Table 2 entry 5). *tert*-Butyl {[3-(4-acetylphenyl)thiophen-2-yl]methyl}(picolinoyl)carbamate (**3f**) gave **5f** in 69% overall yield without affecting the keto group, and the thiophene moiety did not hamper Ni catalysis (Table 2 entry 6). Ethyl picolinate (**6**) was recovered in 72% yield. Furthermore, substrates **4g–h** derived from aromatic amines (aniline and 1-naphthylamine) featuring acetate ester, chloro and SO_2Ph groups also proved to be viable substrates (Table 2 entries 7–8).

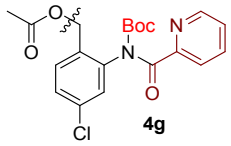
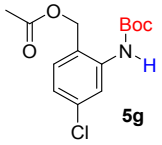
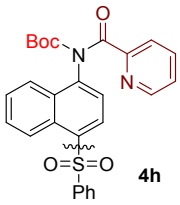
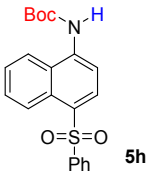
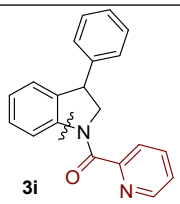
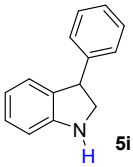
Tertiary amide substrate (3-phenyl-2,3-dihydro-1*H*-indol-1-yl)(pyridin-2-yl)methanone (**3i**) obtained via directed Pd-catalyzed amidation of *N*-(2,2-diphenylethyl)picolinamide (**2i**) cannot be activated via Bocylation. However, *N*-methyl-*N*-phenylarenecarboxamides are also known to be reactive towards oxidative addition.[25a] When we applied our standard reaction condition (without SIPr), only 30% conversion of **3i** was obtained (Table S2 entry 1). The cleavage of *N*-benzoylindoline with methanol by the Garg group gave indoline in 58% yield using the

Ni(cod)$_2$/SIPr system.[25a] Further optimization (Table S2) revealed that a ligand was beneficial in this case. With Ni(cod)$_2$ (15 mol%), terpyridine (15 mol%),[25b] EtOH (30.0 equiv) at 100 °C for 20 h, an optimal yield of **5i** was obtained (80%) with 63% by-product **6** (Table S2 entry 10, Table 2 entry 9).

Table 2. Scope of the Boc activation and subsequent Ni-catalyzed cleavage of *N*-Boc Picolinamides (4) with EtOH.



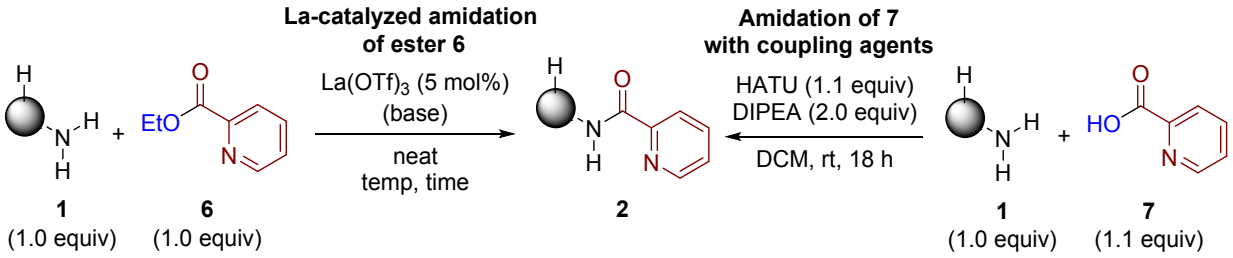
Entry	3	*N*-Boc picolinamides (4)[a]	Yield of 4 (%)[b]	*N*-Boc amines (5)	Yield of 5 (%)[c]	Yield of 6 (%)
1	**3a**	 **4a**	96	 **5a**	90	73
2	**3b**	 **4b**	96	 **5b**	96	87
3	**3c**	 **4c**	97	 **5c**	86	74
4	**3d**	 **4d**	63[d]	 **5d**	94	81
5	**3e**	 **4e**	96[e]	 **5e**	82	72
6	**3f**	 **4f**	86	 **5f**	80	72

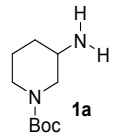
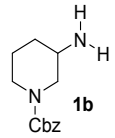
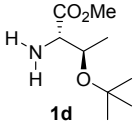
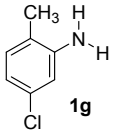
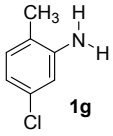
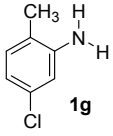
7	**3g**	 **4g**	96	 **5g**	91	75
8	**3h**	 **4h**	92	 **5h**	91	70
9[f]	**3i**	 **3i**	-	 **5i**	80[g]	63[g]

[a] The wavy bond in **4** represents where the C–H functionalization has been performed. [b] Conditions: **3a–h** (2.25–14.71 mmol, 1.0 equiv), DMAP (0.2 equiv), Boc_2O (9.0 equiv), Et_3N (1.1 equiv), THF (0.2 M), 50 °C, 24 h. [c] Conditions: **4a–h** (0.15–1.20 mmol, 1.0 equiv), $Ni(cod)_2$ (10 mol%), EtOH (2.0 equiv), toluene (1.0 M), 80 °C, 15 h. [d] DMAP (0.4 equiv), Et_3N (3.0 equiv), 80 °C. 31% of **3d** was recovered. [e] DMAP (0.4 equiv), Et_3N (4.0 equiv), 80 °C. [f] Reaction product is a tertiary amide, so *N*-Bocylation was not required. [g] Conditions: **3i** (0.2 mmol, 1.0 equiv), $Ni(cod)_2$ (15 mol%), terpyridine (15 mol%), EtOH (30.0 equiv), toluene (0.2 mL), 100 °C, 20 h; 8% **3i** was recovered.

Finally, we explored whether the recovered ethyl picolinate (**6**) could immediately be used as a precursor for the DG introduction by reacting it with amines **1** in the presence of $La(OTf)_3$ catalyst without solvent based on a protocol disclosed by Oshima.[33] This gives immediately access to the substrates **2** for transition metal-catalyzed C(sp^3/sp^2)–H functionalization. The reaction was optimized on *tert*-butyl 3-aminopiperidine-1-carboxylate (**1a**) which is the precursor for substrate **3a** and **3c** (see supporting information Table S3). The reaction temperature was kept above the melting point of the desired product **2a**, to avoid solidification upon product formation. The reaction of **1a** (1.0 equiv) with ethyl picolinate **6** (1.0 equiv) at 100 °C under neat condition gave 70% isolated yield of **2a** (Table 3 entry 1). Similarly, the reaction of **1b** with **6** yielded **2b** in 71% yield (Table 3 entry 2), this time requiring at 130 °C due to the higher melting point of **2b**. With these gratifying results, we applied the reaction condition on some other amines including aromatic and aliphatic primary amines **1**. On *H*-Thr(^{t}Bu)-OMe (**1d**) the required reaction temperature to obtain a liquid is unfortunately too high to avoid epimerization (Table 3 entry 3). Moreover a low yield of target compound was obtained. 5-Chloro-2-methylaniline (**1g**) provided a low yield under the standard conditions (Table 3 entry 4). An additional base (DBU) was therefore used to increase the nucleophilicity of the aromatic amine substrate **1g** and a slight excess of **6** was also required to get full conversion (Table 3 entries 5–6). Eventually, the product **2g** was obtained in 77% isolated yield using 1.2 equiv of **6** and 2.0 equiv of DBU after 22 h (Table 3 entry 6).

Table 3. Amidation of ethyl 2-picolinate (6) and 2-picolinic acid (7) with amines (1)



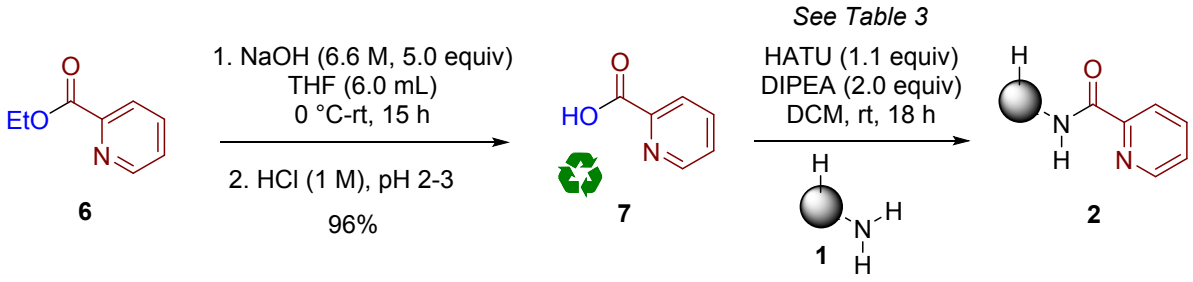
Entry	Amines **1**	La-catalyzed amidation reaction				Classical reaction Yield of **2** (%)[b]
		Temp (° C)	Time (h)	Base	Yield of **2** (%)[a]	
1	 **1a**	100	24	No	70	96
2	 **1b**	130	24	No	71	94
3	 **1d**	130	18	No	30	82[c]
4	 **1g**	120	18	No	27	88
5	 **1g**	120	18	DBU (1.0 equiv)	49[d]	88
6	 **1g**	120	22	DBU (2.0 equiv)	77[d]	88

Isolated yields. [a] Conditions: **1** (1.0 mmol, 1.0 equiv), **6** (1.0 equiv), with or without DBU, $La(OTf)_3$ (5 mol%). [b] Conditions: **1** (1.0 equiv), **7** (1.1 equiv), HATU (1.1 equiv), DIPEA (2.0 equiv), DCM, rt, 18 h. [c] **1d**·HCl was used. [d] 1.2 equiv of **6** was used.

Although the direct La-catalyzed amidation reaction of ethyl 2-picolinote (**6**) with amines **1** is inherently very attractive, it required a reaction temperature above the melting point of product **2** due to the absence of solvent sometimes avoiding applicability. We therefore also looked into the hydrolysis of **6** into 2-picolinic acid (**7**) (Scheme 1).[34] As 2-picolinic acid (**7**) has been used to prepare all PA substrates **2** via coupling with the corresponding amines **1** (see supporting

information and Table 3), it provided an indirect DG recycling strategy. In principle use of water instead of EtOH to cleave **4**, providing immediate access to **7**, would also be interesting. Unfortunately, a reaction starting from model substrate **3a** proved this approach does not work and only substrate was identified, which is not surprising based on the known sensitivity of $Ni(cod)_2$.[35]

Scheme 1. Hydrolysis of ethyl 2-picolinate (6) and recycling of 2-picolinic acid (7)



Conclusion

In conclusion, an efficient two-step protocol for the cleavage of the picolinamide directing group has been developed. The protocol consists of activation via Bocylation followed by Ni-catalyzed esterification of *N*-Boc-picolinamide with ethanol under neutral reaction conditions. *N*-Boc protected amines were isolated in good to excellent yields. A broad range of sensitive functional groups were well tolerated under these reaction conditions. Additionally, the by-product ethyl 2-picolinate formed upon DG cleavage was recovered in good yields and a direct and indirect recycling strategy has been disclosed. It can be expected that the newly developed picolinamide DG cleavage procedure can be applied on other well-known amide based directing groups.

EXPERIMENTAL SECTION

General Considerations

All chemicals and solvents were used as obtained by their respective suppliers, unless otherwise noted. In particular, acetone (99.5+%), dichloromethane (99.8+%), ethyl acetate (99.8+%), ethanol (99.8%), toluene (99.85%, extra dry over molecular sieve) and commercial heptanes (extra pure, used as an eluent in chromatographic purification) were purchased from a commercial source. The latter was distilled prior to use. Ethanol was dried over activated molecular sieve for at least two days prior to use. Water was deionized using a EUROTEC L4 reverse osmosis system. The used water had a conductivity of max. 0.5 µS/cm.

Chromatographic purification was performed using an automated flash chromatography Biotage system utilizing commercially available Silica Flash Cartridges (12, 40 or 80 g) at a flow rate of 20–30 mL/min. TLC analysis was performed using pre-coated TLC aluminium sheets ALUGRAM® SIL G/UV_{254} (layer: 0.20 mm silica gel with fluorescent indicator UV_{254}). The spots were detected with UV light at 254 nm. Melting points were measured on a Melting Point B-545 apparatus and are uncorrected.

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 Fourier Transform NMR spectrometer in $CDCl_3$ at 303 K (unless stated otherwise). Samples were prepared using ca. 10–30 mg of compound dissolved in 1.0 mL of deuterated solvents ($CDCl_3$ or DMSO-d_6). All spectra were referenced either to the TMS reference peak (δ = 0.00 ppm for both ^1H and ^{13}C in $CDCl_3$) or solvent residual peak (δ = 2.51 and 40.02 ppm for ^1H and ^{13}C respectively in DMSO-d_6). Chemical shifts (δ) are reported in ppm; coupling constants (*J*) are reported in Hz; splitting patterns are assigned as s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, or combinations thereof.

High resolution mass spectrometry (HRMS) samples were prepared by dissolving 0.1–5.0 mg of the compound in methanol and further diluting to a concentration of 10^{-5}–10^{-6} M with 50% methanol/50% H_2O/0.1% formic acid. The samples were injected in the MS using a CapLC system and a nanoelectrospray source operated in positive ion mode at a potential of 1.5 or 1.7 kV. The eluent used was 30% A (0.1% formic acid in H_2O) and 70% B (0.1% formic acid in CH_3CN/H_2O-95/5) at a flow rate of 6.0 mL/min. Samples were injected with an interval of 3 min. Before analysis, 2.0 mL of a 0.025% H_3PO_4 solution ($MeOH/H_2O$-50/50) or 10.0 mL of 10^{-6}M deoxyadenosine solution ($MeOH/H_2O$-50/50) was injected as a lock mass. Positive ion mode accurate mass spectra were acquired using a Q-TOF instrument.

Synthetic Procedures and Characterization Data

General Procedure A (Boc activation of picolinamide)

A roundbottom flask was charged with Boc_2O (9.0 equiv), 2-picolinamide substrate **3a-h** (1.0 equiv), DMAP (0.2–0.4 equiv), anhydrous THF (5.0 mL/1.0 mmol) and Et_3N (1.1–4.0 equiv). The flask was attached to a reflux condensor and stirred at 50–80 °C (oil bath) for 24 h under argon (balloon). Upon completion, volatiles were removed under reduced pressure. The crude was diluted with DCM (1x20.0 mL/mmol) and washed with brine (1x20.0 mL/mmol). The organic layer was separated, dried over $MgSO_4$, filtered, evaporated to dryness and purified by automated flash chromatography using heptane/EtOAc as eluent.

General Procedure B (Ni-catalyzed picolinamide esterification)

An oven dried 10 mL pressure vial containing *N*-Boc-picolinamide substrate **4a-h** (1.0 equiv) was charged with $Ni(cod)_2$ (10 mol%) in a glovebox. The vial was sealed with an aluminium crimp cap and removed from the glovebox. Then, toluene (1.0 mL/1.0 mmol) and ethanol (2.0 equiv) were added into the sealed vial under argon (balloon). The closed reaction vial was inserted into an oil bath, preheated at 80 °C, and stirred for 15 h. After cooling to room temperature, the reaction mixture was diluted with DCM (5.0 mL), stirred for 10 min, filtered through a celite bed and washed thoroughly with DCM (30.0 mL). The filtrate was evaporated to dryness under reduced pressure to obtain the crude, which was purified by automated flash chromatography using heptane/EtOAc as eluent.

General Procedure C (La-catalyzed DG introduction via amidation of ethyl 2-picolinate)

The reaction was performed based on a literature procedure.[33] To a Schlenk flask equipped with a stir bar was added $La(OTf)_3$ (5 mol%) and the flask was then flame-dried under vacuum. After cooling to room temperature, the flask was backfilled with argon. Subsequently ethyl 2-picolinate **6** (1.0 equiv) and an amine substrate **1** (1.0 equiv) were added in air, then the flask was flushed with argon and closed. The mixture was stirred at the required temperature for 18–24 h (Table 3). After completion of the reaction time the reaction was allowed to cool to room temperature. The crude was diluted with DCM (20.0 mL/mmol) and washed with brine (20.0 mL/mmol). The organic layer was separated, dried over $MgSO_4$, filtered, evaporated to dryness and purified by automated flash chromatography using heptane/EtOAc as eluent.

Compounds **2a**,[10d] **2b**,[10d] **2d**,[11b] **2e**,[7d] **2f**,[10e] **2g**,[12a] **2h**,[7c] **2i**,[11a] **3a**,[10d] **3c**,[10d] **3d**,[7b] **3e**,[7d] **3f**,[10e] **3h**,[16] **3i**[11a] were synthesized following the respective literature procedures (see SI for schemes, yields and NMR spectra).

Benzyl *cis*-3-[4-(methoxycarbonyl)phenyl]-5-[(pyridine-2-carbonyl)amino]piperidine-1-carboxylate (3b) (SBI-079)

A pressure vial (10 mL) equipped with a magnetic stirring bar was charged with phenyl 3-[(pyridine-2-carbonyl)amino]piperidine-1-carboxylate **2b** (0.14 g, 0.40 mmol, 1.0 equiv), Ag_2CO_3 (0.11 g, 0.40 mmol, 1.0 equiv), 2,6-dimethylbenzoicacid (15.0 mg, 0.10 mmol, 0.25 equiv), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol, 10 mol%), methyl 4-iodobenzoate (0.63 g, 2.40 mmol, 6.0 equiv). All manipulations were performed in air. The vessel was flushed with argon, sealed with an aluminum crimp cap and a securing metal clamp, and was placed in an oil bath preheated to 120 °C and stirred for 24 h. Additionally, the oil bath was covered with aluminum foil to avoid contact with light. After the reaction time, the reaction vessel was removed from the oil bath, cooled to room temperature, diluted with DCM (5.0 mL), stirred for 15 min, and filtered through a pad of Celite, which was additionally rinsed with DCM till the washings became transparent (approx. 50.0 mL). The filtrate was concentrated under reduced pressure. The resulting crude residue was purified by automated flash chromatography (SiO_2, 80 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 50% heptane/50% EtOAc over 90 min followed by 50% heptane/50% EtOAc isocratic over 10 min, 25 mL/min) to give the *title compound* **3b** as a white solid (0.15 g, 78%). No spectroscopic data available in literature.

mp 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.5 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.01–7.98 (m, 3H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.44–7.30 (m, 8H), 5.23-5.14 (m, 2H), 4.58 (d, J = 10.8 Hz, 1H), 4.38 (br s, 1H), 4.28–4.18 (m, 1H), 3.90 (s, 3H), 2.99 (t, J = 11.5 Hz, 1H), 2.78 (t, J = 11.9 Hz, 2H), 2.44–2.38 (m, 1H), 1.75 (q, J = 12.1 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 163.8 (C), 155.1 (C), 149.6 (C), 148.0 (CH), 146.7 (C), 137.4 (CH), 136.6 (C), 130.0 (CH), 129.0 (C), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.1 (CH), 126.4 (CH), 122.3 (CH), 67.5 (CH_2), 52.1 (CH_3), 49.6 (CH_2), 48.3 (CH_2), 46.0 (CH), 41.4 (CH), 38.0 (CH_2) ppm. HRMS (ESI) for $C_{27}H_{28}N_3O_5$ $[M+H]^+$ calcd. 474.2023, found 474.2035.

{4-Chloro-2-[(pyridine-2-carbonyl)amino]phenyl}methyl acetate (3g) (NPR-238)

A mixture of *N*-(5-chloro-2-methylphenyl)picolinamide **2g** (0.60 g, 2.43 mmol, 1.0 equiv), $Pd(OAc)_2$ (55.0 mg, 0.24 mmol, 0.1 equiv), and $PhI(OAc)_2$ (1.96 g, 6.08 mmol, 2.5 equiv) in anhydrous toluene (16.0 mL) was mixed in a 50 mL pressure tube (purged with argon, sealed with screw cap) and heated at 110 °C for 20 hours. The reaction mixture was allowed to cool to room temperature, and was diluted with DCM (40.0 mL). After filtration through celite, the filtrate was concentrated in vacuum and subsequently purified by automated flash chromatography (SiO_2, 40 g cartridge, 90% heptane/10% EtOAc isocratic over 20 min followed by 90% heptane/10% EtOAc to 85% heptane/15% EtOAc over 20 min, followed by 85% heptane/15% EtOAc to 50% heptane/50% EtOAc over 15 min, 30 mL/min) to give the *title compound* **3g** as a white solid (0.40 g, 62%).

mp 107–109 °C (No data in the literature); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (br s, 1H), 8.62–8.60 (m, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.93 (td, J = 7.7, 1.7 Hz, 1H), 7.50 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.13 (dd, J = 8.2, 2.1 Hz, 1H), 5.17 (s 2H), 2.19 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C), 162.3 (C), 149.6 (C), 148.2 (CH), 138.0 (C), 137.8 (CH), 135.5 (C), 131.3 (CH), 126.7 (CH), 124.5 (CH), 124.0 (C), 122.7 (CH), 122.2 (CH), 63.8 (CH_2), 20.8 (CH_3) ppm; HRMS (ESI) for $C_{15}H_{14}ClN_2O_3$ $[M+H]^+$calcd. 305.0687, found 305.0698.

tert-Butyl _cis_-3-[(_tert_-butoxycarbonyl)(pyridine-2-carbonyl)amino]-5-phenylpiperidine-1-carboxylate (4a) (SBI-065)

The *title compound* was synthesized using Boc_2O (1.18 g, 5.40 mmol, 9.0 equiv), amide **3a** (0.23 g, 0.60 mmol, 1.0 equiv), DMAP (15.0 mg, 0.12 mmol, 0.2 equiv), Et_3N (92 µL, 0.66 mmol, 1.1 equiv) and THF (3.0 mL) at 50 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 60% heptane/40% EtOAc over 45 min, 25 mL/min) to give the *title compound* **4a** as a white solid (0.28 g, 96%). No spectroscopic data available in literature.

mp 140-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.4 Hz, 1H), 7.80 (td, J = 7.6, 1.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.38 (ddd, J = 7.4, 4.8, 1.4 Hz, 1H), 7.32–7.20 (m, 5H), 4.59 (tt, J = 11.8, 4.1 Hz, 1H), 4.26 (s, 2H), 3.52 (t, J = 11.0 Hz, 1H), 2.92–2.86 (m, 1H), 2.77 (s, 1H), 2.49 (q, J = 12.2 Hz, 1H), 2.17 (d, J = 12.3 Hz, 1H), 1.48 (s, 9H), 1.16 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C), 154.7 (C), 154.4 (C), 153.1 (C), 148.3 (CH), 142.1 (C), 136.9 (CH), 128.6 (CH), 127.2 (CH), 126.8 (CH), 125.6 (CH), 123.1 (CH), 83.3 (C), 80.0 (C), 53.5 (CH), 49.8 (CH_2), 46.2 (CH_2), 42.8 (CH), 34.9 (CH_2), 28.5 (CH_3), 27.4 (CH_3) ppm. HRMS (ESI) for $C_{27}H_{36}N_3O_5$ $[M+H]^+$ calcd. 482.2649, found 482.2661.

Benzyl _cis_-3-[(_tert_-butoxycarbonyl)(pyridine-2-carbonyl)amino]-5-[4-(methoxycarbonyl)phenyl]piperidine-1-carboxylate (4b) (SBI-081)

The *title compound* was synthesized using Boc_2O (1.18 g, 5.40 mmol, 9.0 equiv), amide **3b** (0.28 g, 0.60 mmol, 1.0 equiv), DMAP (15.0 mg, 0.12 mmol, 0.2 equiv), Et_3N (92 µL, 0.66 mmol, 1.1

equiv) and THF (3.0 mL) at 50 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 50% heptane/50% EtOAc over 40 min followed by 50% heptane/50% EtOAc isocratic over 15 min, 25 mL/min) to give the *title compound* **4b** as a white solid (0.33 g, 96%). No spectroscopic data available in literature.

mp 63-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.80 (t, J = 7.2 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.41–7.31 (m, 8H), 5.17 (s, 2H), 4.63 (t, J = 10.9 Hz, 1H), 4.37 (s, 2H), 3.89 (s, 3H), 3.63 (s, 1H), 2.98–2.87 (m, 2H), 2.62–2.51 (m, 1H), 2.19 (d, J = 11.9 Hz, 1H), 1.14 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C), 166.8 (C), 155.2 (C), 154.3 (C), 152.9 (C), 148.3 (CH), 146.9 (C), 136.9 (CH), 136.7 (C), 130.0 (CH), 128.9 (C), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 125.7 (CH), 123.2 (CH), 83.5 (C), 67.4 (CH_2), 53.2 (CH), 52.0 (CH_3), 49.6 (CH_2), 46.2 (CH_2), 42.6 (CH), 34.5 (CH_2), 27.3 (CH_3) ppm. HRMS (ESI) for $C_{32}H_{36}N_3O_7$ $[M+H]^+$ calcd. 574.2548, found 574.2542.

tert-Butyl _cis_-3-[(_tert_-butoxycarbonyl)(pyridine-2-carbonyl)amino]-5-[1-(benzenesulfonyl)-1_H_-indol-3-yl]piperidine-1-carboxylate (4c) (SBI-194)

The *title compound* was synthesized using Boc_2O (0.49 g, 2.25 mmol, 9.0 equiv), amide **3c** (0.14 g, 0.25 mmol, 1.0 equiv), DMAP (6.10 mg, 0.05 mmol, 0.2 equiv), Et_3N (38 μL, 0.28 mmol, 1.1 equiv) and THF (1.25 mL) at 50 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 50% heptane/50% EtOAc over 60 min, 25 mL/min) to give the *title compound* **4c** as a white solid (0.16 g, 97%). No spectroscopic data available in literature.

mp 91–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.5 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.7 Hz, 2H), 7.81 (dd, J = 7.6, 1.4 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 5.4 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.44–7.40 (m, 3H), 7.36 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.27–7.23 (m, 1H), 4.62 (tt, J = 11.7, 4.0 Hz, 1H), 4.44 (s, 1H), 4.27 (s, 1H), 3.55 (s, 1H), 3.10 (t, J = 11.0 Hz, 1H), 2.67 (t, J = 12.2 Hz, 1H), 2.56 (q, J = 12.2 Hz, 1H), 2.31 (d, J = 12.3 Hz, 1H), 1.50 (s, 9H), 1.17 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C), 154.7 (C), 154.4 (C), 153.0 (C), 148.3 (CH), 138.2 (C), 137.0 (CH), 135.3 (C), 133.8 (CH), 130.0 (C), 129.3 (CH), 126.7 (CH), 125.6 (CH), 125.0 (CH), 123.6 (C), 123.3 (CH), 123.2 (CH), 121.9 (CH), 119.9 (CH), 113.8 (CH), 83.5 (C), 80.2 (C), 53.3 (CH), 48.8 (CH_2), 46.9 (CH_2), 34.1 (CH), 33.4 (CH_2), 28.5 (CH_3), 27.4 (CH_3) ppm. HRMS (ESI) for $C_{35}H_{41}N_4O_7S$ $[M+H]^+$ calcd. 661.2690, found 661.2682.

6-Ethyl 1-methyl (2_S_,3_R_)-3-_tert_-butoxy-2-[(_tert_-butoxycarbonyl)(pyridine-2-carbonyl)amino]hexanedioate (4d) (SBI-205)

The *title compound* was synthesized using Boc_2O (1.81 g, 8.28 mmol, 9.0 equiv), amide **3d** (0.35 g, 0.92 mmol, 1.0 equiv), DMAP (45.0 mg, 0.37 mmol, 0.4 equiv), Et_3N (0.39 mL, 2.76 mmol, 3.0 equiv) and THF (4.6 mL) at 80 °C following the general procedure A. The resulting crude

residue was purified by automated flash chromatography (SiO_2, 80 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 80 min followed by 70% heptane/30% EtOAc isocratic over 20 min, 30 mL/min) to give the *title compound* **4d** as a pale yellow oil (0.28 g, 63%). Additionally, 31% (0.11 g, 0.29 mmol) of the starting material **3d** was recovered. No spectroscopic data available in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62–8.60 (m, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.61 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 4.97 (d, *J* = 9.0 Hz, 1H), 4.54 (ddd, *J* = 8.9, 4.8, 2.4 Hz, 1H), 4.13 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.70 (s, 3H), 2.56 (ddd, *J* = 16.0, 9.4, 6.6 Hz, 1H), 2.42 (ddd, *J* = 16.0, 9.8, 6.1 Hz, 1H), 2.27–2.15 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 9H), 1.17 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 170.9 (C), 169.2 (C), 154.3 (C), 152.8 (C), 148.4 (CH), 136.7 (CH), 125.2 (CH), 122.8 (CH), 83.5 (C), 75.0 (C), 67.9 (CH), 60.3 (CH_2), 59.5 (CH), 52.3 (CH_3), 29.2 (CH_2), 28.5 (CH_3), 28.0 (CH_2), 27.5 (CH_3), 14.2 (CH_3) ppm. HRMS (ESI) for $C_{24}H_{37}N_2O_8$ $[M+H]^+$ calcd. 481.2544, found 481.2526.

Methyl *N*-(*tert*-butoxycarbonyl)-*O*-[*tert*-butyl(dimethyl)silyl]-2,6-dimethyl-*N*-(pyridine-2-carbonyl)-*L*-tyrosinate (4e) (NPR-243)

The *title compound* was synthesized using Boc_2O (2.22 g, 10.17 mmol, 9.0 equiv), amide **3e** (0.50 g, 1.13 mmol, 1.0 equiv), DMAP (55.0 mg, 0.45 mmol, 0.4 equiv), Et_3N (0.64 mL, 4.52 mmol, 4.0 equiv) and THF (5.7 mL) at 80 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 80 g cartridge, 90% heptane/10% EtOAc isocratic over 30 min followed by 90% heptane/10% EtOAc to 50% heptane/50% EtOAc over 30 min followed by 50% heptane/50% EtOAc isocratic over 10 min, 30 mL/min) to give the *title compound* **4e** as a pale yellow oil (0.59 g, 96%). No spectroscopic data available in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 7.71 (td, *J* = 7.7, 1.6 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.33 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1H), 6.42 (s, 2H) 5.43 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.76 (s, 3H), 3.64 (dd, *J* = 14.9, 11.1 Hz, 1H), 3.48 (dd, *J* = 14.9, 4.0 Hz, 1H), 2.33 (s, 6H), 1.04 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C), 170.5 (C), 154.0 (C), 153.7 (C), 152.6 (C), 148.3 (CH), 139.0 (C), 136.5 (CH), 126.7 (C), 125.1 (CH), 122.6 (CH), 119.6 (CH), 83.4 (C), 57.6 (CH), 52.5 (CH_3), 29.5 (CH_2), 27.1 (CH_3), 25.7 (CH_3), 20.3 (CH_3), 18.1 (C), -4.5 (CH_3) ppm. HRMS (ESI) for $C_{29}H_{43}N_2O_6Si$ $[M+H]^+$ calcd. 543.2885, found 543.2880.

***tert*-Butyl {[3-(4-acetylphenyl)thiophen-2-yl]methyl}(pyridine-2-carbonyl)carbamate (4f) (SBI-211)**

The *title compound* was synthesized using Boc_2O (1.64 g, 7.49 mmol, 9.0 equiv), amide **3f** (0.28 g, 0.83 mmol, 1.0 equiv), DMAP (20.0 mg, 0.17 mmol, 0.2 equiv), Et_3N (0.13 mL, 0.92 mmol, 1.1 equiv) and THF (4.2 mL) at 50 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 80 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 50% heptane/50% EtOAc over 60 min followed

by 50% heptane/50% EtOAc isocratic over 20 min, 30 mL/min) to give the *title compound* **4f** as a pale yellow oil (0.31 g, 86%). No spectroscopic data available in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57–8.55 (m, 1H), 8.03 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.66 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.59 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.37 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.27 (d, *J* = 5.1 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 5.27 (s, 2H), 2.63 (s, 3H), 1.12 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7 (C), 171.1 (C), 154.2 (C), 152.6 (C), 148.3 (CH), 141.2 (C), 139.1 (C), 137.0 (C), 136.7 (CH), 135.8 (C), 129.2 (CH), 128.7 (CH), 128.6 (CH), 125.3 (CH), 124.3 (CH), 122.9 (CH), 83.5 (C), 43.1 (CH_2), 27.3 (CH_3), 26.6 (CH_3) ppm. HRMS (ESI) for $C_{24}H_{25}N_2O_4S$ $[M+H]^+$ calcd. 437.1530, found 437.1527.

{2-[(*tert*-Butoxycarbonyl)(pyridine-2-carbonyl)amino]-4-chlorophenyl}methyl acetate (4g) (SBI-204)

The *title compound* was synthesized using Boc_2O (3.16 g, 14.47 mmol, 9.0 equiv), amide **3g** (0.49 g, 1.61 mmol, 1.0 equiv), DMAP (39.0 mg, 0.32 mmol, 0.2 equiv), Et_3N (0.25 mL, 1.77 mmol, 1.1 equiv) and THF (8.0 mL) at 50 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 80 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 75% heptane/25% EtOAc over 60 min followed by 75% heptane/25% EtOAc isocratic over 10 min followed by 75% heptane/25% EtOAc to 50% heptane/50% EtOAc over 15 min, 30 mL/min) to give the *title compound* **4g** as a white solid (0.62 g, 96%). No spectroscopic data available in literature.

mp 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.5 Hz, 1H), 7.85 (td, *J* = 7.6, 1.6 Hz, 1H), 7.80 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.47–7.43 (m, 2H), 7.40–7.38 (m, 2H), 5.24 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 1.93 (s, 3H), 1.20 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C), 170.6 (C), 153.5 (C), 152.2 (C), 148.5 (CH), 138.2 (C), 136.9 (CH), 134.6, (C) 133.3 (C), 131.1 (CH), 130.0 (CH), 129.2 (CH), 125.9 (CH), 123.4 (CH), 83.9 (C), 62.3 (CH_2), 27.4 (CH_3), 20.7 (CH_3) ppm. HRMS (ESI) for $C_{20}H_{22}ClN_2O_5$ $[M+H]^+$, calcd 405.1212, found 405.1213.

***tert*-Butyl [4-benzenesulfonyl)naphthalen-1-yl](pyridine-2-carbonyl)carbamate (4h) (SBI-212)**

The *title compound* was synthesized using Boc_2O (3.21 g, 14.71 mmol, 9.0 equiv), amide **3h** (0.64 g, 1.64 mmol, 1.0 equiv), DMAP (40.0 mg, 0.33 mmol, 0.2 equiv), Et_3N (0.25 mL, 1.80 mmol, 1.1 equiv) and THF (8.2 mL) at 50 °C following the general procedure A. The resulting crude residue was purified by automated flash chromatography (SiO_2, 80 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 40% heptane/60% EtOAc over 60 min followed by 40% heptane/60% EtOAc isocratic over 30 min, 30 mL/min) to give the *title compound* **4h** as a white solid (0.73 g, 92%). No spectroscopic data available in literature.

mp 189–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72–8.68 (m, 2H), 8.59 (d, *J* = 7.8 Hz, 1H), 8.33–8.29 (m, 1H), 8.01–7.98 (m, 2H), 7.89–7.82 (m, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.61–7.56 (m, 2H), 7.55–7.51 (m, 1H), 7.50–7.45 (m, 3H), 1.18 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2

(C), 153.3 (C), 152.5 (C), 148.5 (CH), 141.5 (C), 141.3 (C), 137.1 (CH), 136.5 (C), 133.2 (CH), 131.9 (C), 129.8 (CH), 129.7 (C), 129.2 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 126.1 (CH), 125.5 (CH), 124.8 (CH), 123.8 (CH), 123.6 (CH), 84.2 (C), 27.3 (CH_3) ppm. HRMS (ESI) for $C_{27}H_{25}N_2O_5S$ $[M+H]^+$ calcd. 489.1479, found 489.1495.

tert-Butyl _cis_-3-[(_tert_-butoxycarbonyl)amino]-5-phenylpiperidine-1-carboxylate (5a) (SBI-223)

The *title compound* was synthesized using *N*-Boc-picolinamide **4a** (96.0 mg, 0.20 mmol, 1.0 equiv), $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol%), EtOH (23.0 μL, 0.40 mmol, 2.0 equiv) and toluene (0.2 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% EtOAc isocratic over 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5a** as a white solid (68.0 mg, 90%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 73% yield (22.0 mg). No spectroscopic data available in literature.

mp 137-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.25–7.19 (m, 3H), 4.43–4.38 (m, 2H), 4.24 (s, 1H), 3.65 (s, 1H), 2.79 (tt, *J* = 11.8, 3.7 Hz, 1H), 2.62 (t, *J* = 11.8 Hz, 1H), 2.42 (t, *J* = 11.8 Hz, 1H), 2.30 (d, *J* = 12.5 Hz, 1H), 1.47 (s, 9H), 1.45 (s, 9H), 1.44 (q, *J* = 12.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (C), 154.5 (C), 142.0 (C), 128.6 (CH), 127.0 (CH), 126.9 (CH), 80.0 (C), 79.6 (C), 49.7 (CH_2), 48.8 (CH_2), 47.4 (CH), 41.5 (CH), 38.9 (CH_2), 28.42 (CH_3), 28.37 (CH_3) ppm. HRMS (ESI) for $C_{21}H_{33}N_2O_4$ $[M+H]^+$ calcd. 377.2435, found 377.2451.

Benzyl _cis_-3-[(_tert_-butoxycarbonyl)amino]-5-[4-(methoxycarbonyl)phenyl]piperidine-1-carboxylate (5b) (SBI-235)

The *title compound* was synthesized using *N*-Boc-picolinamide **4b** (0.143 g, 0.25 mmol, 1.0 equiv), $Ni(cod)_2$ (6.88 mg, 0.025 mmol, 10 mol%), EtOH (29.0 μL, 0.50 mmol, 2.0 equiv) and toluene (0.25 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% EtOAc isocratic over 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5b** as a white solid (0.112 g, 96%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 87% yield (33.0 mg). No spectroscopic data available in literature.

mp 124-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.36–7.30 (m, 5H), 7.26 (d, *J* = 7.4 Hz, 2H), 5.15 (t, *J* = 11.0 Hz, 2H), 4.60 (d, *J* = 7.4 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.32 (s, 1H), 3.90 (s, 3H), 3.69 (s, 1H), 2.87 (t, *J* = 12.2 Hz, 1H), 2.71 (s, 1H), 2.54 (t, *J* = 12.2 Hz, 1H), 2.30 (d, *J* = 12.2 Hz, 1H), 1.51 (q, *J* = 12.2 Hz, 1H), 1.43 (s, 9H) ppm. ^{13}C NMR (101 MHz,

$CDCl_3$) δ 166.8 (C), 155.1 (C), 155.0 (C), 146.8 (C), 136.6 (C), 130.0 (CH), 128.9 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.1 (CH), 79.7 (C), 67.4 (CH_2), 52.1 (CH_3), 49.5 (CH_2), 48.7 (CH_2), 47.2 (CH), 41.5 (CH), 38.4 (CH_2), 28.3 (CH_3) ppm. HRMS (ESI) for $C_{26}H_{33}N_2O_6$ $[M+H]^+$ calcd. 469.2333, found 469.2328.

tert-Butyl _cis_-3-[(_tert_-butoxycarbonyl)amino]-5-[1-(benzenesulfonyl)-1_H_-indol-3-yl]piperidine-1-carboxylate (5c) (SBI-233)

The *title compound* was synthesized using *N*-Boc-picolinamide **4c** (0.100 g, 0.151 mmol, 1.0 equiv), $Ni(cod)_2$ (4.16 mg, 0.015 mmol, 10 mol%), EtOH (18.0 μL, 0.303 mmol, 2.0 equiv) and toluene (0.15 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% ethyl acetate isocratic over 10 min followed by 70% heptane/30% ethyl acetate to 50% heptane/50% ethyl acetate over 10 min, 25 mL/min) to give the *title compound* **5c** as a white solid (72.0 mg, 86%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 74% yield (17.0 mg). No spectroscopic data available in literature.

mp 106–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.54–7.51 (m, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.33–7.30 (m, 2H), 7.26–7.22 (m, 1H), 4.45–4.39 (m, 3H), 3.70 (br, s, 1H), 3.02–2.96 (m, 1H), 2.60–2.43 (m, 3H), 1.50–1.45 (m, 19H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (C), 154.5 (C), 138.2 (C), 135.3 (C), 133.8 (CH), 129.9 (C), 129.3 (CH), 126.7 (CH), 125.1 (CH), 123.8 (C), 123.3 (CH), 121.7 (CH), 119.7 (CH), 113.8 (CH), 80.3 (C), 79.7 (C), 49.0 (2 x CH_2), 47.1 (CH), 37.6 (CH_2), 32.9 (CH), 28.43 (CH_3), 28.39 (CH_3) ppm. HRMS (ESI) for $C_{29}H_{38}N_3O_6S$ $[M+H]^+$ calcd. 556.2476, found 556.2477.

6-Ethyl 1-methyl (2_S_,3_R_)-3-_tert_-butoxy-2-[(_tert_-butoxycarbonyl)amino]hexanedioate (5d) (SBI-237)

The *title compound* was synthesized using *N*-Boc-picolinamide **4d** (0.15 g, 0.312 mmol, 1.0 equiv), $Ni(cod)_2$ (8.59 mg, 0.031 mmol, 10 mol%), EtOH (36.0 μL, 0.624 mmol, 2.0 equiv) and toluene (0.31 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% EtOAc isocratic over 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5d** as a colorless oil (0.11 g, 94%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 81% yield (38.0 mg). No spectroscopic data available in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (d, J = 9.6 Hz, 1H), 4.31 (d, J = 9.8 Hz, 1H), 4.14 (q, J = 6.9 Hz, 2H), 4.06 (t, J = 6.7 Hz, 1H), 3.71 (s, 3H), 2.45–2.30 (m, 2H), 1.86 (dd, J = 14.2, 7.0 Hz, 2H), 1.45 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C),

172.0 (C), 156.1 (C), 79.9 (C), 74.5 (C), 70.6 (CH), 60.4 (CH_2), 56.2 (CH), 52.1 (CH_3), 30.3 (CH_2), 29.1 (CH_2), 28.4 (CH_3), 28.3 (CH_3), 14.2 (CH_3) ppm. HRMS (ESI) for $C_{18}H_{34}NO_7$ $[M+H]^+$ calcd. 377.2330, found 377.2335.

Methyl *N*-(*tert*-butoxycarbonyl)-*O*-[*tert*-butyl(dimethyl)silyl]-2,6-dimethyl-*L*-tyrosinate (5e) (SBI-227)

The *title compound* was synthesized using *N*-Boc-picolinamide **4e** (0.13 g, 0.24 mmol, 1.0 equiv), $Ni(cod)_2$ (6.59 mg, 0.024 mmol, 10 mol%), EtOH (28.0 µL, 0.479 mmol, 2.0 equiv) and toluene (0.24 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% EtOAc isocratic over 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5e** as a colorless oil (86.0 mg, 82%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 72% yield (26.0 mg). No spectroscopic data available in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 2H), 5.05 (d, *J* = 7.4 Hz, 1H), 4.48 (q, *J* = 8.0 Hz, 1H), 3.61 (s, 3H), 2.99 (d, *J* = 7.4 Hz, 2H), 2.27 (s, 6H), 1.38 (s, 9H), 0.97 (s, 9H), 0.17 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 154.9 (C), 153.9 (C), 138.3 (C), 126.1 (C), 119.7 (CH), 79.8 (C), 53.1 (CH), 52.1 (CH_3), 32.8 (CH_2), 28.3 (CH_3), 25.7 (CH_3), 20.3 (CH_3), 18.2 (C), -4.4 (CH_3) ppm. HRMS (ESI) for $C_{23}H_{40}NO_5Si$ $[M+H]^+$ calcd. 438.2670, found 438.2675.

***tert*-Butyl {[3-(4-acetylphenyl)thiophen-2-yl]methyl}carbamate (5f) (SBI-248)**

The *title compound* was synthesized using *N*-Boc-picolinamide **4f** (0.14 g, 0.32 mmol, 1.0 equiv), $Ni(cod)_2$ (8.82 mg, 0.032 mmol, 10 mol%), EtOH (37.0 µL, 0.64 mmol, 2.0 equiv) and toluene (0.32 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% ethyl acetate over 60 min followed by 70% heptane/30% EtOAc isocratic for 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5f** as a colorless oil (85.0 mg, 80%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 72% yield (35.0 mg). No spectroscopic data available in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 5.3 Hz, 1H), 7.06 (d, *J* = 5.2 Hz, 1H), 4.91 (br, s, 1H), 4.53 (d, *J* = 4.6 Hz, 2H), 2.62 (s, 3H), 1.45 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6 (C), 155.4 (C), 140.8 (C), 138.5 (C), 138.2 (C), 135.8 (C), 129.0 (CH), 128.8 (CH), 128.7 (CH), 124.2 (CH), 79.9 (C), 38.4 (CH_2), 28.4 (CH_3), 26.6 (CH_3) ppm. HRMS (ESI) for $C_{18}H_{22}NO_3S$ $[M+H]^+$ calcd. 332.1315, found 332.1321.

{2-[(*tert*-Butoxycarbonyl)amino]-4-chlorophenyl}methyl acetate (5g) (SBI-232)

The *title compound* was synthesized using *N*-Boc-picolinamide **4g** (0.24 g, 0.59 mmol, 1.0 equiv), $Ni(cod)_2$ (16.0 mg, 0.059 mmol, 10 mol%), EtOH (69.0 μL, 1.18 mmol, 2.0 equiv) and toluene (0.59 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% EtOAc isocratic over 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5g** as a white solid (0.16 g, 91%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 75% yield (67.0 mg). No spectroscopic data available in literature.

mp 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.1 Hz, 1H), 7.52 (br, s, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.03 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.05 (s, 2H), 2.09 (s, 3H), 1.54 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C), 152.9 (C), 138.6 (C), 135.7 (C), 132.1 (CH), 123.5 (CH), 123.2 (C), 121.8 (CH), 81.0 (C), 63.1 (CH_2), 28.3 (CH_3), 20.9 (CH_3) ppm. HRMS (ESI) for $C_{14}H_{19}ClNO_4$ $[M+H]^+$ calcd. 300.0997, found 300.0983.

tert-Butyl [4-benzenesulfonyl)naphthalen-1-yl]carbamate (5h) (SBI-225)

The *title compound* was synthesized using *N*-Boc-picolinamide **4h** (98.0 mg, 0.20 mmol, 1.0 equiv), $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol%), EtOH (23.0 μL, 0.40 mmol, 2.0 equiv) and toluene (0.20 mL) following the general procedure B. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% EtOAc over 60 min followed by 70% heptane/30% EtOAc isocratic over 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5h** as a white solid (70.0 mg, 91%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 70% yield (21.0 mg). No spectroscopic data available in literature.

mp 190–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67–8.62 (m, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.93–7.90 (m, 2H), 7.87–7.84 (m, 1H), 7.56–7.40 (m, 5H), 7.26 (br, s, 1H), 1.57 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5 (C), 142.2 (C), 139.4 (C), 132.8 (CH), 131.2 (CH), 129.9 (C), 129.4 (C), 129.0 (CH), 128.2 (CH), 127.2 (CH), 126.8 (CH), 125.3 (C), 125.2 (CH), 120.6 (CH), 114.2 (CH), 81.9 (C), 28.3 (CH_3) ppm. HRMS (ESI) for $C_{21}H_{22}NO_4S$ $[M+H]^+$ calcd. 384.1264, found 384.1289.

3-Phenyl-2,3-dihydro-1*H*-indole (5i) (SBI-242)

An oven dried 10 mL pressure vial containing tertiary amide **3i** (60.0 mg, 0.20 mmol, 1.0 equiv) and terpyridine (7.0 mg, 15 mol%) was charged with $Ni(cod)_2$ (15 mol%) in a glovebox. The vial was sealed with an aluminium crimp cap and removed from the glovebox. Then, toluene (0.2 mL) and ethanol (0.35 mL, 6.0 mmol, 30.0 equiv) were added into the sealed vial under argon (balloon). The reaction vial was inserted into an oil bath, preheated at 100 °C, and stirred for 20 h. After cooling to room temperature, the reaction mixture was diluted with DCM (5.0 mL), stirred for 10

min, filtered through a celite bed and washed thoroughly with DCM (30.0 mL). The filtrate was evaporated to dryness under reduced pressure. The resulting crude residue was purified by automated flash chromatography (SiO_2, 40 g cartridge, 100% heptane isocratic over 5 min followed by 100% heptane to 70% heptane/30% ethyl acetate over 60 min followed by 70% heptane/30% EtOAc isocratic for 10 min followed by 70% heptane/30% EtOAc to 50% heptane/50% EtOAc over 10 min, 25 mL/min) to give the *title compound* **5i** as a pale yellow oil (31.0 mg, 80%). Additionally, ethyl 2-picolinate **6** was obtained as a by-product in 63% yield (19.0 mg) and unreacted starting material **3i** was recovered in 8% yield (5.0 mg). Spectroscopic data are in accordance with the literature.[11a]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5H), 7.06 (tt, *J* = 7.5, 0.9 Hz, 1H), 6.90 (dt, *J* = 7.7, 1.0 Hz, 1H), 6.71–6.68 (m, 2H), 4.47 (t, *J* = 9.0 Hz, 1H), 3.91 (t, *J* = 9.1 Hz, 1H), 3.75–3.63 (m, 1H), 3.48 (t, *J* = 8.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (C), 143.6 (C), 132.3 (C), 128.6 (CH), 128.1 (CH), 127.7 (CH), 126.7 (CH), 125.0 (CH), 119.0 (CH), 109.7 (CH), 56.6 (CH_2), 48.7 (CH) ppm. HRMS (ESI) for $C_{14}H_{14}N$ $[M+H]^+$ calcd. 196.1121, found 196.1123.

Ethyl pyridine-2-carboxylate (or ethyl 2-picolinate) (6) (SBI-072-2)

The *title compound* was obtained as a by-product during the Ni-catalyzed *N*-Boc-picolinamide esterification reactions following the general procedure B. Spectroscopic data are in accordance with the literature.[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.3 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.85 (td, *J* = 7.7, 1.5 Hz, 1H), 7.48 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C), 149.9 (CH), 148.4 (C), 137.0 (CH), 126.8 (CH), 125.1 (CH), 61.9 (CH_2), 14.4 (CH_3) ppm. HRMS (ESI) for $C_8H_{10}NO_2$ $[M+H]^+$ calcd. 152.0706, found 152.0713.

Pyridine-2-carboxylic acid (or 2-picolinic acid) (7) (NPR-256)

The *title compound* was synthesised following a literature procedure.[34] Ethyl pyridine-2-carboxylate **6** (0.50 g, 6.62 mmol, 1.0 equiv) was dissolved in 6.0 mL THF (0.55 M) at 0 °C in a 100 mL round-bottom flask. To the resulting solution aq. NaOH solution (2.5 mL, 6.6 M, 5.0 equiv) was added dropwise and stirred for 15 h under air at room temperature. After starting materials were consumed (checked by TLC), water (20.0 mL) was added. The reaction mixture was washed with ethyl acetate (1x20.0 mL). The aqueous solution was acidified (pH 2 to 3) with 1 M HCl (aq). The resulting suspension was concentrated under vacuum to remove water and evaporated to dryness to give a white solid. Ethanol (1x40.0 mL) and pentane (1x40.0 mL) were added to the resulting solid, and the resulting suspension was sonificated and subsequently filtered through filter paper to remove inorganic salts. The filtrate was evaporated to dryness to give *title compound* **7** as white solid (0.39 g, 96% yield with >95% NMR purity). The spectral data are in accordance with the literature.[36]

mp 129–131 °C (lit.[34] 130–134 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J = 4.2 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.98 (td, J = 7.7, 1.6 Hz, 1H) 7.64–7.61 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7 (C), 149.8 (CH), 149.1(C), 138.0 (CH), 127.4 (CH), 125.0 (CH), ppm. HRMS (ESI) for $C_6H_6NO_2$ $[M+H]^+$ calcd. 124.0399, found 124.0389.

ASSOCIATED CONTENT

Supporting Information.

Optimization tables, reaction schemes, ^{1}H, ^{13}C NMR and 2D spectra of all compounds are shown in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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