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FULL PAPER

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Design of Chiral NHC-Carboxylates as Potential Ligands for Pd-Catalyzed Enantioselective C–H Activation

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Dedicated to Prof. *E. Peter Kündig* on the occasion of his 75th birthday

Despite numerous efforts, the synthesis of scalemic carbo- and heterocycles through Pd^0-catalyzed C(sp^3)–H activation employing chiral ancillary ligands or chiral bases is still limited. Inspired by the recently reported outstanding performance of IBiox-type NHC ligands and bifunctional ligands in similar transformations, a new class of bifunctional NHC-ligands bearing a pendant carboxylate group was designed. A library of 10 imidazolium-carboxylic acids was obtained in five to six steps from enantiopure L-*tert*-leucinol. In addition, four well-defined Pd(DMBPA)-NHC palladacycles were synthesized in good to excellent yields from the corresponding imidazolium precursors. These complexes were tested in a prototypical C(sp^3)–H arylation reaction, and the most active one afforded the indoline product in low yield but significant enantioselectivity. These new bifunctional NHCs could find broader applications in catalytic enantioselective transformations occurring under milder conditions.

Keywords: asymmetric catalysis, bifunctional ligands, C–H activation, N-heterocyclic carbenes, palladium.

Introduction

In the past 20 years, transition-metal catalyzed C–H activation reactions have been established as powerful synthetic tools.[1] However, in order to cleave non-activated C–H bonds, a high kinetic barrier has to be overcome, hence requiring the use of highly reactive transition-metal catalysts.[2] In addition, the presence of multiple C–H bonds of similar strength and steric environment often results in chemo-, regio- and stereoselectivity issues. In the past years, a great number of strategies and catalysts were developed to address these issues, and an array of atom- and step-economical methods suitable for the synthesis or late-stage modification of complex molecules were developed.[3–7] Despite intense recent developments, the control of enantioselectivity in C–H bond activation remains challenging and is still limited to certain motifs.[8–10]

In 2011, the groups of *Kündig*[11] and *Kagan*[12] independently reported the first example of Pd^0-catalyzed enantioselective C(sp^3)–H activation initiated by oxidative addition and producing chiral indolines. A high enantioinduction was achieved using a chiral NHC or phosphine ligand, respectively. After these initial reports, diverse enantioselective transformations proceeding through Pd^0-catalyzed C(sp^3)–H activation were published.[13] Different classes of chiral ligands, including phosphoramidites,[14] phosphines,[15,16] phosphonites,[17] diazaphospholidines,[18] and NHCs[11] were employed in order to reach a high enantioselectivity for different classes of products. Alternatively, the use of a chiral base in combination with an achiral ligand is also able to deliver enantioselectivity in Pd^0/Pd^{II} catalyzed C(sp^3)–H arylation.[12,15] By exploiting this concept, we reported a highly enantioselective synthesis of indolines using a chiral binol-derived phosphate in combination with an achiral phosphine ligand.[19] Despite important efforts, only a relatively

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small variety of cyclic systems can be accessed to date through enantioselective Pd^0-catalyzed C(sp^3)–H activation, and hence more broadly applicable chiral catalysts are still needed.

Our group recently showed the beneficial effect of bifunctional ligands in Pd^0-catalyzed enantioselective desymmetrizing C(sp^2)–H activation for the synthesis of 5,6-dihydrophenanthridines[20] and chiral warped molecules.[21] The designed phosphine ligands (**1**) based on a binaphthyl scaffold incorporate a carboxylate group, which acts as the base to promote the C–H activation step occurring through the concerted metalation-deprotonation (CMD) mechanism (*Figure 1*).[22] It is assumed that the high enantioinduction results from a highly ordered transition state, which allows this system to outperform the corresponding monofunctional ligands. However, we found that this bifunctional phosphine ligand was not sufficiently reactive to activate the stronger C(sp^3)–H bonds. In parallel, our group recently reported that bis-oxazoline-derived (IBiox)[23–25] NHC ligands (**2**) exhibit both a high reactivity and enantioselectivity in the challenging arylation of enantiotopic methylene C–H bonds.[26] Motivated by these results, we thought to exploit the outstanding reactivity of IBiox-type ligands in C(sp^3)–H activation to design bifunctional ligands **3** incorporating both a chiral oxazoline ring and a carboxylate group. Amino acid-derived chiral NHC-carboxylates (**4**), wherein the stereogenic center and carboxylate group are located on the same side of the imidazole ring, were previously reported by *Baslé*, *Mauduit* and coworkers. These NHCs were employed in enantioselective Cu-catalyzed reactions[27,28] as well as in Rh-catalyzed C–H borylation,[29,30] hence demonstrating the potential of bifunctional NHC-carboxylate ligands in catalysis.[31–33] We surmised that ligand **3**, wherein the chiral substituent and the carboxylate group are located on opposite sides of the imidazole ring, would be well suited to the enantiodetermining C–H activation step (see the transition-state model in *Figure 1*), with the rigid oxazoline ring providing enantioselectivity and the carboxylate arm providing both reactivity and sufficient flexibility to adapt to the substrate.

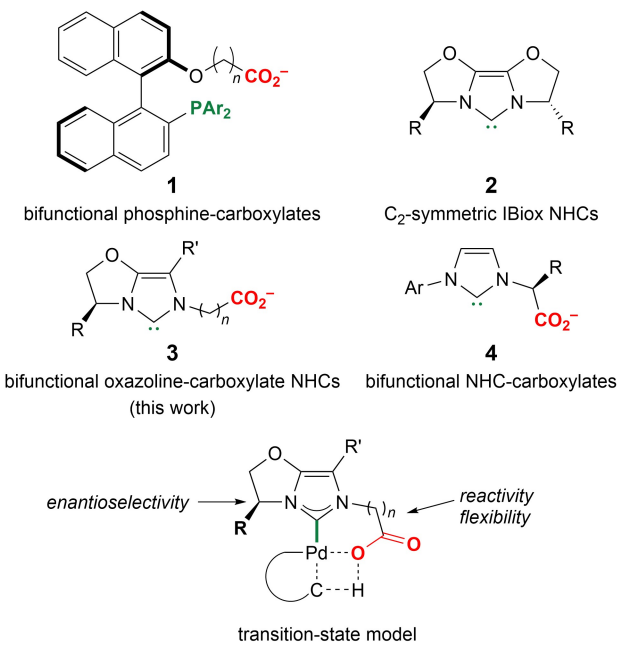
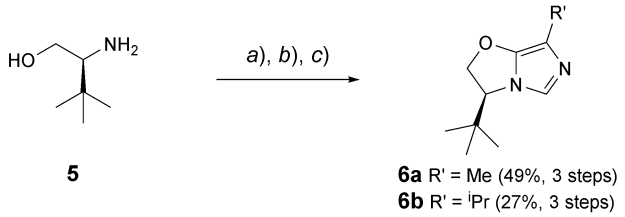


Figure 1. Bifunctional phosphine-carboxylate and NHC-carboxylate ligands.

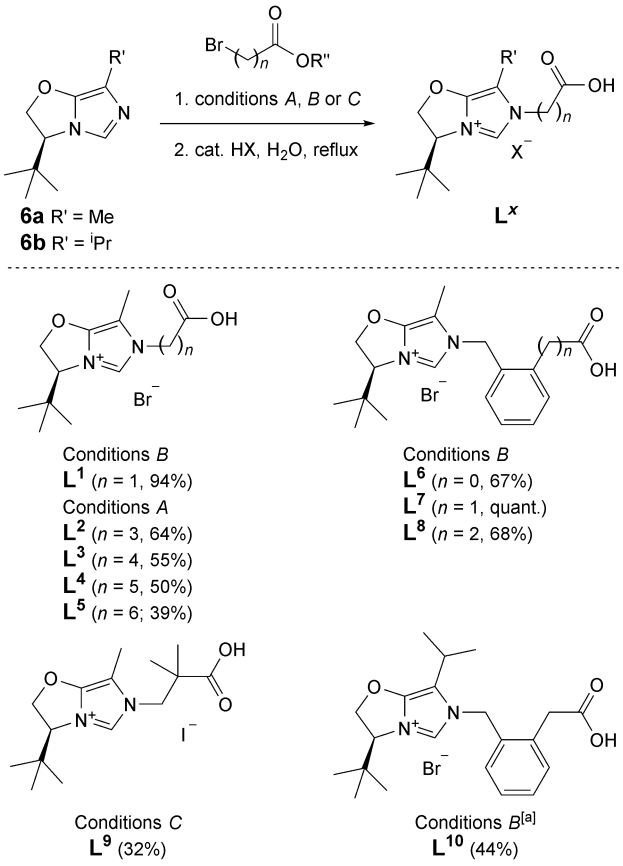
Results and Discussion

The oxazoline-fused imidazole cores of the target ligands (**6a** and **6b**) were synthesized in three steps from enantiopure L-*tert*-leucinol, taking inspiration from a precedent by *Yoshida*, *Yanagisawa* and coworkers (*Scheme 1*).[34] The R′ substituent (R′ = Me, ^{i}Pr) was previously shown to be necessary for the imidazole ring formation and serves as further handle to modulate the steric properties of the bifunctional ligand.

The installation of the carboxylic acid-bearing side arm from **6a** required some optimization (*Scheme 2*). The linear alkyl linkers were installed upon stirring with excess alkyl bromide in acetonitrile during seven



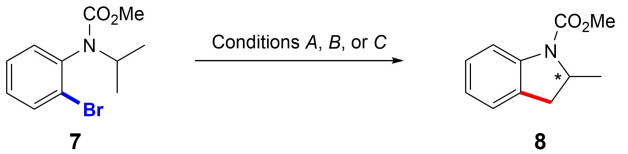
Scheme 1. Synthesis of the oxazolidine-fused imidazole core. *a*) R′ = Me: NMM (1.01 equiv.), *N*-formyl-L-alanine (1.0 equiv.), isobutyl chloroformate (1.01 equiv.), CH_2Cl_2, −15 °C, 15 min, then **5** (1.05 equiv.), −15 to 25 °C, 3 h, 85%; R′ = ^{i}Pr: NMM (1.1 equiv.), *N*-formyl-L-valine (1.1 equiv.), isobutyl chloroformate (1.01 equiv.), THF, −15 °C, 15 min, then **5** (1.0 equiv.), −15 to 25 °C, 16 h, 78%. *b*) R′ = Me: Et_3N (4.3 equiv.), DMAP (0.02 equiv.), *p*-toluenesulfonyl chloride (1.2 equiv.), CH_2Cl_2, 25 °C, 16 h, 92%; R′ = ^{i}Pr: Et_3N (4.3 equiv.), DMAP (0.02 equiv.), *p*-toluenesulfonyl chloride (1.01 equiv.), $C_2H_4Cl_2$, 25 °C, 1 h, then 84 °C, 16 h, 56%. *c*) R′ = Me: P_2O_5 (2.0 equiv.), toluene, 100 °C, 48 h, 63%; R′ = ^{i}Pr: P_2O_5 (3.0 equiv.), toluene, 100 °C, 48 h, 62%. NMM = *N*-methylmorpholine.



Scheme 2. Synthesis of a library of NHC precursors. Conditions *A*: alkyl bromide (1.5 equiv.), MeCN, 25 °C, 7 d. Conditions *B*: alkyl- or benzyl bromide (1.1 equiv.), MeCN, 70 °C, 16 h. Conditions *C*: alkyl triflate (1.5 equiv.), MeCN, 70 °C, 16 h, then 5 equiv. NaI, acetone, 25 °C, 16 h.[a] 48 h at 70 °C.

days at room temperature. More activated electrophiles (benzyl bromides or α-bromoester) reacted at 70 °C in 16 h. Of note, the use of the corresponding carboxylic acids led to protonation, which further slowed down the alkylation rate, and increasing the temperature resulted in a slow degradation. In the case of linear alkyl bromides, elevated temperatures (> 40 °C) led to byproducts resulting from the deprotonation at the α position to the ester, and additives such as Et_3N did not show any beneficial effect. Then, all esters (**13**, **14**, **15**, **16** and **18**) were further hydrolyzed to give the desired NHC imidazolium salt precursors under acidic conditions. As a result, we obtained a library of five imidazolium salts (**L**^{1}–**L**^{5}) with a linear linker [$(CH_2)_nCO_2H$, $n = 1$, 3–6], three (**L**^{6}–**L**^{8}) incorporating a benzene ring with different chain lengths ($CH_2Ar(CH_2)_nCO_2H$, $n = 0$–2), and a neopentyl linker mimicking pivalic acid (**L**^{9}) in moderate to excellent yields. In addition, analogue **L**^{10} bearing an isopropyl group instead of a methyl group on the imidazolium ring was synthesized from **6b**.

The synthesized imidazolium precursors were then evaluated in the Pd^0-catalyzed desymmetrizing C-(sp^3)–H arylation leading to indolines, which was employed as a prototypical enantioselective reaction (*Scheme 3*).[11,12,15,19] In many Pd-catalyzed reactions engaging NHC ligands, the imidazolium salt can be directly added to the mixture containing a Pd source and a base, hence forming the active Pd^0-NHC complex *in situ*.[35,36] Unfortunately, only a low reactivity and no enantioinduction were observed by simply engaging a mixture of the imidazolium salt, a Pd source such as Pd_2dba_3 and a carbonate base, despite extensive experimentation (*Scheme 3*, Conditions *A*). Pd^{II}-(π-allyl) complexes are standard Pd precatalysts in Pd/NHC-catalyzed C–H activation, but they need to be activated *in situ* to generate the active Pd^0-NHC species. Typically, an additive such as pivalate[11,26,37] or *tert*-butoxide[38] is introduced for this purpose. Running the reaction with these additives slightly improved the yield, but the product was completely racemic (Conditions *B*). Various imidazolium salts of our library performed similarly in terms of reactivity and enantioselectivity. At this point, it was questioned whether the active complex was formed under the employed conditions, or if some undefined Pd species were causing the low rate of product formation. The free carboxylate group in our newly designed ligand is the main difference with the IBiox ligands. Considering this, we presumed that this functional group was the reason for the impeded *in situ* Pd^0-NHC complex formation. In order to facilitate this process, we turned our attention towards the synthesis of the corresponding Ag-NHC complexes, which are prone to undergo transmetalation with metals such as



Scheme 3. First evaluation of the newly designed imidazole-carboxylates in the enantioselective synthesis of indoline **8**. Conditions *A*: Pd_2dba_3 (5 mol-%), **L**^{x} (10 mol-%), K_2CO_3 or Cs_2CO_3 (1.5 equiv.), solvent, 160 °C, 16 h. Conditions *B*: [Pd(π-cinnamyl)Cl]$_2$ (5 mol-%), **L**^{x} (10 mol-%), additive (KOPiv, CsOPiv, KO^{t}Bu or CsO^{t}Bu, 10 mol-%), K_2CO_3 or Cs_2CO_3 (1.5 equiv.), solvent, 160 °C, 16 h. Conditions *C*: 1. Ag_2O (5 mol-%), **L**^{x} (10 mol-%), CH_2Cl_2, 25 °C, 16 h; 2. Pd_2dba_3 or [Pd(π-cinnamyl)Cl]$_2$ (5 mol-%), Cs_2CO_3 (1.5 equiv.), CsO^{t}Bu (10 mol-%), mesitylene, 160 °C, 16 h.

Pd.[39,40] We decided to test this approach in the synthesis of indoline **8** (Conditions *C*). To access the silver-NHC-complexes, imidazolium salts were charged with Ag_2O in a catalysis tube in the dark and stirred for 2–24 h at room temperature. The crude Ag complexes were then engaged in the reaction together with the substrate, a stoichiometric base, a Pd source and an additive, and was stirred at 160 °C for 16 h. Unfortunately, low yields and almost no enantioselectivity (18%, 52:48 e.r. for $\mathbf{L^7}$) were again observed using $[Pd(\pi\text{-cinnamyl})Cl]_2$ as the Pd source. Interestingly, using Pd_2dba_3 as the precatalyst in combination with the Ag-NHC complex resulted in a noticeable enantioinduction (64:36 e.r. for $\mathbf{L^7}$), albeit with a low yield (10%). In the latter case the active Pd-NHC complex was presumably formed, albeit in a very inefficient way.

These results led us to consider the synthesis of stable well-defined Pd-complexes with our newly developed NHC-carboxylate ligands. Unfortunately, all attempts at synthesizing [Pd(π-allyl)L] or [Pd(π-cinnamyl)L] complexes either directly from the imidazolium-carboxylic acid precursor or from a protected acid followed with deprotection failed and complex mixtures were observed. We concluded that the resulting carboxylate allyl complex is unstable, probably due to the intramolecular attack of the carboxylate onto the π-allyl ligand, initiating further decomposition (*Figure 2*).

We then became interested in the use of palladacycles as precatalyst instead of the more common Pd^{II}-NHC precomplexes. In a seminal work, *Hermann* and *Beller* successfully applied cyclopalladated phosphine ligands in the *Mizoroki-Heck* reaction.[41] Since this initial report, this class of Pd-precursors has emerged as an attractive stable and readily activated alternative to more commonly used Pd precomplexes.[42–44] In particular, the *Nolan* group reported an IPr-palladacycle complex, which was employed as a very active precatalyst in the cross-coupling of aryl chlorides and amines as well as in the α-arylation of ketones.[45] In this work, the *N*,*N*-dimethyl[1,1′-biphenyl]-2-amine (DMBPA) NHC-palladacycle was synthesized by reacting the free NHC with the corresponding Pd-dimer in good yield. Inspired by these results, we first generated the corresponding Ag-NHC complexes by treatment of the imidazolium salts with Ag_2O. The obtained crude silver complexes were directly engaged in the transmetalation with the DMBPA μ-chloro dimeric Pd complex in THF at room temperature overnight. Following this procedure, Pd complexes $\mathbf{C^1}$–$\mathbf{C^4}$ were isolated in good yields (*Scheme 4*). Other imidazolium salts described in *Scheme 1* were also used as precursors but, despite repeated efforts, they afforded complex mixtures (as monitored by NMR), and the corresponding palladacyclic complexes could not be isolated and characterized without ambiguity.

The single crystal X-ray diffraction analysis of complexes $\mathbf{C^1}$ and $\mathbf{C^3}$ was successfully performed and revealed dimeric and monomeric structures in the solid state, respectively (*Figures 3* and *4*). This observation is not surprising since the monomeric structure should be disfavored for a short linker due to strain and favored with a longer linker. In both complexes, the NHC ligand is located *trans* to the amino group and the carboxylate is bound to the Pd center *trans* to the aryl ligand (NHC–Pd–O_2C angles: 91.7°, $\mathbf{C^1}$; 88.8°,

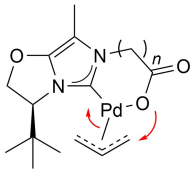
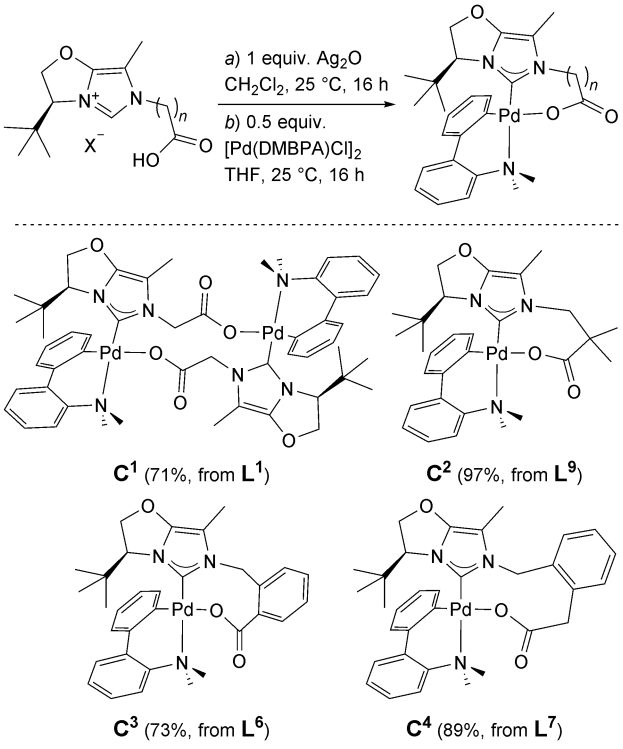


Figure 2. Proposed initial decomposition of bifunctional [Pd(π-allyl)NHC] complexes.



Scheme 4. Synthesis of bifunctional NHC-Pd^{II} palladacyclic complexes $\mathbf{C^1}$–$\mathbf{C^4}$.

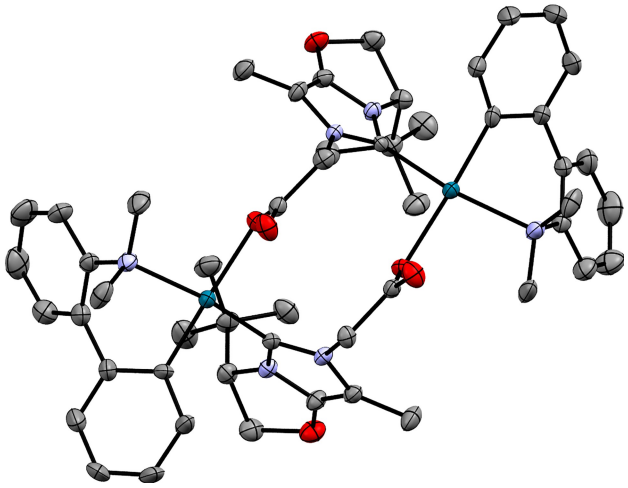


Figure 3. ORTEP representation of the X-ray crystal structure of the dimeric complex **C[1]** (ellipsoids shown at 50% probability). H-atoms were omitted for clarity.

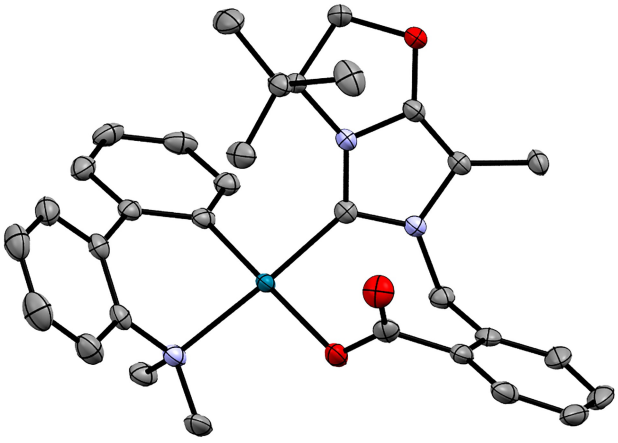


Figure 4. ORTEP representation of the X-ray crystal structure of complex **C[3]** (ellipsoids shown at 50% probability). H-atoms were omitted for clarity.

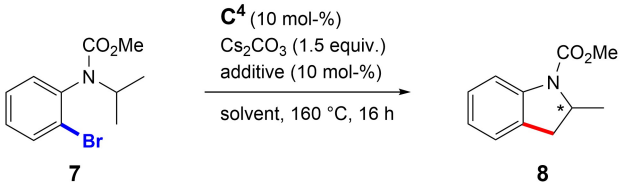
C[3]) in a standard square-planar geometry. The biphenyl scaffold is twisted, due to the steric bulk at the oxazoline ring, similar to previous observations with other NHC ligands.[45] Complexes **C[2]** and **C[4]** occurred as monomers similar to **C[3]**, as indicated by mass spectrometry, but did not afford crystals suitable for X-ray diffraction analysis.

With these well-defined Pd^{II}-complexes in hand, we turned our attention towards their application in enantioselective C(sp^3)–H activation (*Table 1*). Running the standard reaction with 10 mol-% of complex **C[4]** in the presence of 1.5 equiv. Cs_2CO_3 and 10 mol-% of CsO^tBu as activator[45] at 160 °C in mesitylene for 16 h yielded 20% of almost racemic indoline (*Entry 1*). This low yield and low enantioinduction indicate again a possible inefficient generation of the active chiral Pd^0-NHC complex. Examination of the solvent effect showed a similar behavior in apolar aromatic solvents. A slight increase in yield was observed in ethers such as THF, Bu_2O and anisole (*Entry 2*), while full decomposition occurred in polar aprotic solvents (*e.g.*, DMSO, *Entry 3*). However, the enantioselectivity did not improve noticeably in any case. We were curious to know if the originally employed *tert*-butoxide was suitable for the activation of the complex under the current reaction conditions. Omitting CsO^tBu actually gave the same results, hence showing the inaptitude of this reagent at activating the precomplex (*Entry 4*). Replacing cesium *tert*-butoxide with sodium formate resulted in low yield and formation of the racemic product (*Entry 5*), and a similar result was obtained with diphenylaniline (*Entry 6*). Hydrazine and morpholine were likewise unable to provide a more active catalyst, and only led to traces of product (*Entries 7* and *8*). Surprisingly, the addition of 20 mol-% HFIP increased the enantiomeric ratio to 78:22, albeit with a low yield (20%; *Entry 9*). Encouraged by this result, we tried to optimize the reaction conditions. Various solvents were tested (*e.g.*, anisole, *Entry 10*), but comparable results to mesitylene were at best obtained. Moreover, further variation of the employed stoichiometric base did not show any beneficial effect on the yield or enantioselectivity.

At this point, we assumed that these unsuccessful results were again the result of the difficult generation of an active Pd^0-NHC complex prior to the substrate oxidative addition. To further investigate this preactivation, we performed some NMR experiments. Complex **C[1]** was dissolved in degassed C_6D_6 and various activating agents were added in order to monitor the modification of the *N*,*N*-dimethylbiphenylamine motif. The addition of hydrazine, DIBAL–H, and LiHMDS resulted in the immediate full decomposition of the complex. As expected from the above results (*Table 1*, *Entry 4*), the addition of CsO^tBu did not result in any change, neither at room temperature nor at 70 °C. Interestingly, when HFIP was added, a visible change in the proton signals of the NHC core and HFIP was observed (see *Figure S1*). We propose that HFIP coordinates to the Pd-center and forms a hydrogen bond with the carboxylic group. This intermediate might stabilize the complex and therefore play a beneficial role in the Pd complex activation.

Finally, applying the optimized conditions to the four different complexes **C[1]**–**C[4]** gave low yields for **C[1]** and **C[4]** (13% and 20%, resp., *Table 2*, *Entries 1* and *4*),

Table 1. Effect of solvents and additives in the enantioselective C(sp^3)–H arylation.



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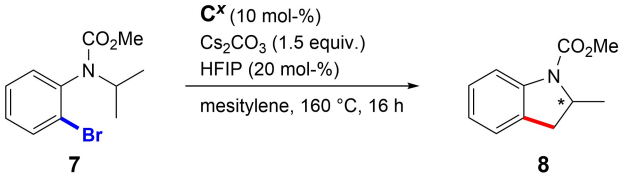
Entry	Solvent[a]	Additive[b]	NMR Yield [%][c]	e.r.[d]
1	mesitylene	CsO^tBu	20	55:45
2	anisole	CsO^tBu	43	55:45
3	DMSO	CsO^tBu	0	–
4	mesitylene	–	21	55:45
5	mesitylene	HCO_2Na	16	52:48
6	mesitylene	Ph_2NH	32	52:48
7	mesitylene	N_2H_2	<5	–
8	mesitylene	morpholine	<5	–
9	mesitylene	HFIP[e]	20	78:22
10	anisole	HFIP[e]	24	69:31

[a]0.1 M. [b]10 mol-%. [c]Using trichloroethylene as internal standard. [d]Determined by HPLC on a chiral stationary phase. [e]20 mol-%.

Table 2. Evaluation of the synthesized complexes in the enantioselective C(sp^3)–H arylation.



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Entry	Complex	^{1}H-NMR Yield [%][a]	e.r.[b]
1	C^1	13	56:44
2	C^2	<5	n.d.
3	C^3	<5	n.d.
4	C^4	20	78:22

[a]Using trichloroethylene as internal standard. [b]Determined by HPLC on a chiral stationary phase.

whereas traces of product were observed with complexes C^2 and C^3 (*Entries 2* and *3*). In addition, the enantioselectivity induced by C^4 was significantly higher than with C^1 (C^4, e.r. 78:22; C^1, e.r. 56:44). Therefore, the nature of the linker separating the carboxylate group from the imidazole core seems to have a significant effect on the catalyst performance.

Upon further analysis of the Pd complexes, we realized that they decomposed in the solid state far below the reaction temperature (C^1: ≥120 °C; C^2: ≥80 °C; C^3: ≥110 °C; C^4: ≥90 °C). This degradation could explain the low reactivity observed under the applied reaction conditions. Unfortunately, reducing the reaction temperature to 140 °C resulted in traces of indoline **8**.

Conclusions

A library of 10 imidazolium-carboxylic acids with different linkers (five linear, four incorporating a benzene ring, and one neopentyl) was synthesized from enantiopure L-*tert*-leucinol in five to six steps. Four well-defined Pd(DMBPA)NHC palladacycles were obtained from the corresponding imidazolium salts in good to excellent yield and were characterized. The direct use of the imidazolium salts in a prototypical Pd^0-catalyzed C(sp^3)–H arylation reaction only resulted in low reactivity and enantio-induction. Attempts at employing the corresponding Pd(DMBP)NHC palladacycles as precatalysts were modestly successful. HFIP was required as an additive to obtain the indoline product in moderate but significant enantioselectivity

(e.r. 78:22), albeit in low yield. HFIP seems to form a H-bonding network, which stabilizes the complex and limits its decomposition. Further investigations revealed the thermal instability of these palladacycles, which likely explains their poor performance in C-(sp^3)–H activation performed at high temperatures. In light of these results, we believe that these bifunctional NHC precursors could find applications in enantioselective transformations performed under milder conditions, either as ligands[27–32] or as organocatalysts.[46–48]

Experimental Section

General Information

All reactions were performed in pre-dried glassware under positive pressure of argon unless otherwise mentioned. All reactions involving air-sensitive materials were carried out in pre-dried glassware under an argon atmosphere by using *Schlenk* techniques employing double-line argon-vacuum lines and working in an argon-filled glovebox. Analytical thin layer chromatography (TLC) was performed using pre-coated *Merck* silica gel *60 F254* plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains ($KMnO_4$ and phosphomolybdic acid). Flash column chromatography (FC) was performed using *Silicycle SiliaFlash P60* (230–400 mesh) with the indicated solvent system. Anhydrous solvents were obtained from a solvent purification system equipped with activated alumina and copper columns. The solvents were degassed by three cycles of freeze-pump-thaw and stored in single-necked flasks equipped with a *J-Young PTFE* valve (or similar) when necessary. Chemical reagents were purchased from *Merck* (*Sigma–Aldrich*), *Acros Organics*, *Alfa Aesar*, *Apollo scientific* and *Fluorochem* and used as received without further purification unless otherwise stated. HPLC Analyses were performed using a *Shimadzu Prominence* system with *SIL-20 A* auto sample, *CTO-20AC* column oven, *LC-20AD* pump system, *DGU-20 A3* degasser and *SPD-M20 A* Diode Array or UV/VIS detector. The following chiral column from *Daicel Chemical Industries* was used: *OJ-H* (*Chiralcel®*) in 4.6×250 mm size. Melting points were obtained on a *Büchi* melting point *M-565* and are uncorrected. IR Spectra were recorded on an *ATR Varian Scimitar 800* and are reported in reciprocal centimeters [cm^{-1}]. Nuclear magnetic resonance spectra were recorded on a *Bruker Advance 400* (400 MHz) and *Advance 500* (500 MHz) in deuterated chloroform (residual peaks ^1H δ 7.26 ppm, ^{13}C δ 77.16 ppm), deuterated acetonitrile (residual peaks ^1H δ 1.94 ppm, ^{13}C δ 1.32 ppm) or deuterated dichloromethane (residual peaks ^1H δ 5.32 ppm, ^{13}C δ 54.00 ppm) unless otherwise noted. Data are reported in parts per million [ppm] as follows: chemical shift, multiplicity (*s* = *singlet*, *d* = *doublet*, *t* = *triplet*, *q* = *quartet*, *quint* = *quintuplet*, *sept* = *septuplet*, *m* = *multiplet* and br. = broad signal), coupling constants in Hz and integration. High resolution mass spectra were recorded by Dr. *M. Pfeffer* and *S. Mittelheisser* (Department of Chemistry, University of Basel) on a *Bruker maXis 4G QTOF ESI* mass spectrometer. Optical rotations were measured on an *Anton Paar MCP 100 Polarimeter* in a 0.7 mL micro cuvette (cell length 100 mm) with NaD-Line (λ = 589 nm). The concentration (*c*) was given in g/100 mL. X-ray crystallographic analyses were performed by Dr. *A. Prescimone* (Department of Chemistry, University of Basel).

Procedures

Methyl (2-bromophenyl)propan-2-ylcarbamate (**7**),[19] $[Pd(DMBPA)Cl]_2$,[49] CsO^tBu[50], and (2*S*)-2-Amino-3,3-dimethylbutan-1-ol (**5**)[51] were synthesized according to literature.

General Procedure A: Imidazole Alkylation

Bromo alkyl ester (1.5 equiv.) was added to a 0.36 M solution of imidazole (**6a**, 1.0 equiv.) in dry MeCN under Ar. The mixture was stirred for 7 d or to completion at 25 °C. The solvent was removed under reduced pressure. A minimal amount of CH_2Cl_2 was added to dissolve the crude mixture, and Et_2O was added to precipitate the product (usually orange sticky oil). The solvent was removed and the residue further dried. Then, H_2O (0.1 M imidazolium solution) and two drops of HBr (48 wt-% in H_2O, cat.) were added to the crude mixture and the mixture was refluxed for 3 h. The mixture was allowed to cool down to 25 °C and the water was removed under reduced pressure. The crude mixture was again dissolved in a minimum amount of CH_2Cl_2 and precipitated with Et_2O. The solvent was removed, and the obtained residue washed again with Et_2O. All solvent residues were removed under reduced pressure to afford the corresponding carboxyl-imidazolium salts. If needed, the obtained products were further purified by FC (MeOH/CH_2Cl_2/AcOH 10:90:1).

General Procedure B: Imidazole Alkylation

Activated bromo alkyl- or benzyl ester (1.1 equiv.) was added to a 0.36 M solution of imidazole (**6a** or **6b**, 1.0 equiv.) in dry MeCN under Ar. The mixture was stirred for 16 h at 70 °C. The solvent was removed under reduced pressure. A minimal amount of CH_2Cl_2 was added to dissolve the crude mixture, and Et_2O was added to precipitate the product (usually orange sticky oil or off white solid). The solvent was removed and the residue further dried. Then, H_2O (0.1 M imidazolium solution) and two drops of HBr (48 wt-% in H_2O, cat.) were added to the crude mixture and the mixture was refluxed for 2 to 48 h. The mixture was allowed to cool down to 25 °C, and the water was removed under reduced pressure. The crude mixture was again dissolved in a minimum amount of CH_2Cl_2 and precipitated with Et_2O. The solvent was removed, and the obtained residue washed again with Et_2O. All solvent residues were removed under reduced pressure to afford the corresponding carboxyl-imidazolium salts. If needed, the obtained products were further purified by FC ($MeOH/CH_2Cl_2$/AcOH 10:90:1).

General Procedure C: C–H Activation Protocol with Ag-NHC Complex

In the dark, Ag_2O (0.1 equiv.) was added to the corresponding $\mathbf{L}^x$ (0.1 equiv.) in a catalysis tube covered with aluminum foil in the glovebox. The tube was closed with a septum and removed from the glovebox. Dry CH_2Cl_2 (1 mL/0.1 mmol $\mathbf{L}^x$) was added under argon and the resulting mixture was stirred at 25 °C for 16 h. The mixture was filtered over *Celite* and the solvent removed under reduced pressure. The crude mixture was transferred into a new catalysis tube, which was then introduced into the glovebox. Substrate (1.0 equiv.), Cs_2CO_3 (1.5 equiv.), Pd-source (10 mol-% Pd), and additive (10 mol-%) were charged into the tube containing the crude Ag-NHC complex which was then sealed. The tube was taken out of the glovebox and dry and degassed solvent (1 mL/0.1 mmol substrate) was added. The mixture was stirred at 160 °C for 16 h. The mixture was allowed to cool down to 25 °C, filtered over a plug of *Celite*, and the solvent removed under reduced pressure. ^{1}H-NMR yields were determined of the crude mixture. After further purification by FC, the e.r. was determined by HPLC on chiral stationary phase.

General Procedure D: Complex Formation

Following a modified procedure.[45] In the dark, Ag_2O (1.0 equiv.) was added to the corresponding imidazolium salt ($\mathbf{L}^x$, 1.0 equiv.) in a reaction flask covered in aluminum foil in the glovebox. The flask was sealed with a septum and removed from the glovebox. Dry CH_2Cl_2 was added and the resulting mixture was stirred at 25 °C under Ar for 16 h. The mixture was filtered over *Celite*, and the solvent removed under reduced pressure. Pd-dimer[49] (0.5 equiv.) was added to the crude mixture, and the flask was evacuated and backfilled with Ar three times. Dry THF was added and the resulting suspension stirred at 25 °C for 16 h. The crude was filtered over a plug of *Celite* and all solvents were removed under reduced pressure. Hexane was added to precipitate the product. The product was filtered and washed with hexane.

General Procedure E: C–H Activation Protocol with $\mathbf{C}^x$

In the glovebox, substrate (1.0 equiv.), Cs_2CO_3 (1.5 equiv.), complex ($\mathbf{C}^x$, 10 mol-%), and solid additive (10 mol-%) were charged into a microwave vial. The vial was sealed and taken out of the glovebox. Dry and degassed solvent (1 mL/0.1 mmol substrate), and liquid additives (10- or 20 mol-%) were added. The mixture was stirred at 160 °C for 16 h. The mixture was allowed to cool down to 25 °C, filtered over a plug of *Celite*, and the solvent was removed under reduced pressure. ^{1}H-NMR yields were determined of the crude mixture. After further purification by FC, the e.r. was determined by HPLC on chiral stationary phase.

N^2-Formyl-*N*-[(2*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-L-alaninamide (**9**). *N*-Methylmorpholine (0.99 mL, 9.04 mmol, 1.01 equiv.) was added to a suspension of formyl-L-alanine (prepared following a known procedure[52]) (1.05 g, 8.95 mmol, 1.00 equiv.) in dry CH_2Cl_2 (20 mL) under Ar and was stirred at 25 °C until a homogeneous mixture was observed. The resulting mixture was cooled down to −15 °C and isobutyl chloroformate (1.19 mL, 9.04 mmol, 1.01 equiv.) was added dropwise. After 15 min at the same temperature, (2*S*)-2-amino-3,3-dimethylbutan-1-ol (**5**, 1.10 g, 9.39 mmol, 1.05 equiv.) was added. The resulting mixture was allowed to warm to 25 °C and stirred for further 3 h at this temperature. The solvent was removed under reduced pressure. The crude mixture was purified by FC (silica gel, gradient, acetone/CH_2Cl_2 1:1 to 1:0, R_f = 0.20 (acetone/CH_2Cl_2 1:1)), affording the title compound (**9**, 1.64 g,

7.58 mmol, 85%) as a colorless solid. ^{1}H-NMR (500 MHz, (D_6)DMSO): 8.23 (*d*, *J* = 7.7, 1 H); 7.96 (*s*, 1 H); 7.46 (*d*, *J* = 9.5, 1 H); 4.45–4.38 (*m*, 1 H); 4.37 (*t*, *J* = 5.3, 1 H); 3.59–3.52 (*m*, 2 H); 3.32–3.26 (*m*, 1 H); 1.20 (*d*, *J* = 6.9, 3 H); 0.84 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_6) DMSO):171.9; 160.6; 60.5; 58.6; 47.0; 33.7; 26.8; 18.6. $[\alpha]_D^{20} = -54.0$ (*c* = 1.01, MeOH). NMR data are consistent with literature data.[53]

***N*-{(1*S*)-1-[(4*S*)-4-*tert*-Butyl-4,5-dihydro-1,3-oxazol-2-yl]ethyl}formamide** (**10**). Et_3N (4.80 mL, 34.20 mmol, 4.30 equiv.) was added dropwise to a suspension of N^2-formyl-*N*-[(2*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-L-alaninamide (**9**, 1.72 g, 7.95 mmol, 1.00 equiv.), DMAP (0.02 g, 0.12 mmol, 0.02 equiv.), and *p*-toluenesulfonyl chloride (1.82 g, 9.54 mmol, 1.20 equiv.) in dry CH_2Cl_2 (88 mL) under Ar. The resulting mixture was stirred at 25 °C for 16 h. The mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The phases were separated, and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, AcOEt, $R_f = 0.18$) affording the title compound (**10**, 1.45 g, 7.31 mmol, 92%) as a yellow oil as a diastereomeric mixture (d.r. 8.9:1.1). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.18 (*s*, 1 H); 6.65 (br. *s*, 1 H); 4.71 (*quint*, *J* = 7.0, 1 H); 4.24 (*t*, *J* = 9.4, 1 H); 4.14 (*t*, *J* = 8.3, 1 H); 3.87–3.79 (*m*, 1 H); 1.43 (*d*, *J* = 6.9, 3 H); 0.87 (*s*, 9 H). ^{13}C-NMR (101 MHz, $CDCl_3$): 167.2; 160.4; 75.4; 69.9; 42.7; 33.7; 25.8; 19.4. $[\alpha]_D^{20} = -87.7$ (*c* = 1.63, CH_2Cl_2) of the diastereomeric mixture. ^{13}C-NMR spectrum is consistent with literature data.[53]

(3*S*)-3-*tert*-Butyl-7-methyl-2,3-dihydroimidazo-[5,1-*b*][1,3]oxazole (**6a**). P_2O_5 (6.64 g, 46.8 mmol, 2.0 equiv.) was added to a solution of *N*-{(1*S*)-1-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]ethyl}formamide (**10**, 4.63 g, 23.4 mmol, 1.0 equiv.) in dry toluene (260 mL) under Ar and was then stirred at 100 °C for 48 h. The resulting mixture was allowed to cool down to 25 °C and the solvent was decanted. 1 M HCl (65 mL) was added to the crude mixture. After all solid has dissolved, a 20 wt-% aqueous solution of KOH was added until the mixture had a pH of 12. The resulting mixture was extracted with CH_2Cl_2 three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, AcOEt, $R_f = 0.12$) affording the title compound (**6a**, 2.66 g, 14.8 mmol, 63%) as a yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.06 (*s*, 1 H); 4.92 (*dd*, *J* = 9.1, 8.1, 1 H); 4.80 (*dd*, *J* = 9.2, 4.3, 1 H); 4.09 (*dd*, *J* = 8.0, 4.3, 1 H); 2.07 (*s*, 3 H); 0.98 (*s*, 9 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 149.3; 122.7; 105.3; 78.5; 65.1; 33.9; 25.6; 11.1. $[\alpha]_D^{20} = +17.6$ (*c* = 1.17, $CHCl_3$). ^{13}C-NMR is consistent with literature data.[53]

***N*^{2}-Formyl-*N*-[(2*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-L-valinamide** (**11**). *N*-Methylmorpholine (2.43 mL, 22.1 mmol, 1.10 equiv.) was added to a suspension of formyl-L-valine (prepared following procedure[52]) (2.77 g, 21.1 mmol, 1.10 equiv.) in dry THF (70 mL) under Ar and was stirred at 25 °C until a homogeneous mixture was observed. The resulting mixture was cooled down to −15 °C and isobutyl chloroformate (2.55 mL, 19.4 mmol, 1.01 equiv.) was added dropwise. After 15 min at the same temperature, (2*S*)-2-asmino-3,3-dimethylbutan-1-ol (**5**, 2.25 g, 19.2 mmol, 1.00 equiv.) was added. The resulting mixture was allowed to warm to 25 °C and stirred at the same temperature for 16 h. The solvent was evaporated under reduced pressure before water (25 mL) was added. The precipitate was filtered off, washed with water, and AcOEt and further dried to afford the title compound (**11**, 3.67 g, 15.0 mmol, 78%) as a colorless powder. ^{1}H-NMR (500 MHz, (D_6) DMSO): 8.14 (*d*, *J* = 9.0, 1 H); 8.03 (*d*, *J* = 1.8, 1 H); 7.53 (*d*, *J* = 9.5, 1 H); 4.33 (br. *s*, 1 H); 4.30–4.24 (*m*, 1 H); 3.61 (*ddd*, *J* = 9.5, 7.9, 3.9, 1 H); 3.55 (*dt*, *J* = 10.7, 3.1, 1 H); 3.28 (*qd*, *J* = 9.1, 8.3, 4.4, 1 H); 1.95 (*sept*, *J* = 6.7, 1 H); 0.88 (*d*, *J* = 6.8, 3 H); 0.86–0.82 (*m*, 12 H). ^{13}C-NMR (126 MHz, (D_6)DMSO): 170.8; 160.8; 60.6; 58.5; 56.4; 33.7; 30.5; 26.9; 19.3; 18.1. HR-ESI-MS: 267.1684 ($C_{12}H_{24}N_2NaO_3^+$, $[M+H]^+$; calc. 267.1679). IR (neat): 3342, 3260, 3096, 2965, 2890, 2361, 1650, 1580, 1393, 1238, 670, 629. M.p. 204 °C. $[\alpha]_D^{20} = -44.9$ (*c* = 1.04, MeOH).

***N*-{(1*S*)-1-[(4*S*)-4-*tert*-Butyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropyl}formamide** (**12**). Et_3N (4.45 mL, 31.70 mmol, 4.30 equiv.) was added dropwise to a suspension of N^2-formyl-*N*-[(2*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-L-valinamide (**11**, 1.80 g, 7.37 mmol, 1.00 equiv.), DMAP (0.01 g, 0.11 mmol, 0.02 equiv.), and *p*-toluenesulfonyl chloride (1.42 g, 7.44 mmol, 1.01 equiv.) in dry dichloroethane (255 mL) under Ar. The resulting mixture was stirred for 1 h at 25 °C, then refluxed for 16 h. The mixture was cooled down to 25 °C, diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The phases were separated, and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude mixture was purified by FC (silica gel, AcOEt, $R_f = 0.24$) affording the title compound (**12**, 0.93 g, 4.12 mmol, 56%) as a yellow oil (diastereomeric mixture, d.r. 82:18). Major diastereoisomer: ^{1}H-NMR (500 MHz, $CDCl_3$): 8.25 (*s*, 1 H); 6.35 (*d*, *J* = 8.6, 1 H); 4.68 (*ddt*, *J* = 8.8, 4.8, 0.8, 1 H); 4.21 (*dd*, *J* = 10.1, 8.8, 1 H); 4.11 (*dd*, *J* = 8.8, 7.8, 1 H); 3.84 (*ddd*, *J* = 10.1, 7.8, 0.8, 1 H); 2.16 (*quintd*, *J* = 6.9, 4.7, 1 H); 0.95 (*d*, *J* = 6.9, 3 H); 0.93 (*d*, *J* = 6.9, 3 H); 0.87 (*s*, 9 H).^{13}C-NMR (126 MHz, $CDCl_3$): 165.8; 160.7; 75.4; 69.5; 51.3; 33.8; 31.6; 25.9; 18.9; 17.9. Minor diastereoisomer: ^{1}H-NMR (500 MHz, $CDCl_3$): 8.04 (*d*, *J* = 11.9, 1 H); 6.04–5.95 (*m*, 1 H); 4.28–4.23 (*m*, 1 H); 4.06 (*dd*, *J* = 13.7, 8.7, 1 H); 3.95 (*dd*, *J* = 10.0, 6.3, 1 H); 3.88 (*dd*, *J* = 9.3, 1.2, 1 H); 2.08–2.02 (*m*, 1 H); 0.97 (*d*, *J* = 6.8, 3 H); 0.98–0.95 (*m*, 3 H); 0.88 (*s*, 9 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 164.9; 163.8; 75.8; 69.4; 56.3; 33.7; 31.9; 26.0; 19.3; 17.8. HR-ESI-MS: 227.1753 ($C_{12}H_{23}N_2O_2^+$, $[M+H]^+$; calc. 227.1754). IR (neat): 3261, 2961, 2873, 2361, 2340, 1664, 1531, 1479, 1386, 1210, 985, 641. $[\alpha]_D^{20} = -81.1$ ($c = 0.99$, $CHCl_3$) of the diastereomeric mixture.

(3*S*)-3-*tert*-Butyl-7-(propan-2-yl)-2,3-dihydroimidazo[5,1-*b*][1,3]oxazole (**6b**). P_2O_5 (382 mg, 2.69 mmol, 3.0 equiv.) was added to a solution of *N*-{(1*S*)-1-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropyl}formamide (**12**, 203 mg, 0.89 mmol, 1.0 equiv.) in dry toluene (11 mL) under Ar and was then stirred at 100 °C for 48 h. The resulting mixture was allowed to cool down to 25 °C and the solvent was decanted. 1 M HCl (3.8 mL) was added to the crude mixture. After all solid has dissolved, a 20 wt-% aqueous solution of KOH was added until the mixture had a pH of 12. The resulting mixture was extracted with CH_2Cl_2 three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, AcOEt, $R_f = 0.17$) affording the title compound (**6b**, 116 mg, 0.56 mmol, 62%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.15 (*s*, 1 H); 4.92 (*t*, *J* = 8.8, 1 H); 4.80 (*dd*, *J* = 9.2, 4.2, 1 H); 4.09 (*ddd*, *J* = 8.0, 4.2, 1.3, 1 H); 2.83 (*sept*, *J* = 7.3, 6.8, 1 H); 1.23 (*d*, *J* = 7.3, 6.8, 6 H); 0.98 (*s*, 9 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 148.2; 122.6; 115.9; 78.5; 65.0; 34.0; 26.3; 25.7; 22.1; 22.1. HR-ESI-MS: 209.1653 ($C_{12}H_{21}N_2^+$, $[M+H]^+$; calc. 209.1648). IR (neat): 2967, 2905, 2361, 2340, 1700, 1633, 1470, 1386, 1066, 364. M.p. 47 °C. $[\alpha]_D^{20} = +24.4$ ($c = 0.96$, MeCN).

(3*S*)-3-*tert*-Butyl-6-(carboxymethyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^1**). The title compound (**L^1**, 159 mg, 0.46 mmol, 92%) was obtained as an off-white solid following *General Procedure B* using the corresponding imidazole (**6a**, 90 mg, 0.50 mmol, 1.0 equiv.) and ethyl bromoacetate (0.06 mL, 0.55 mmol, 1.1 equiv.) as alkylating agent. The hydrolysis took 2 h under reflux. ^{1}H-NMR (500 MHz, (D_3)MeCN): 8.60 (*s*, 1 H); 5.13–4.96 (*m*, 4 H); 4.69 (*dd*, *J* = 8.1, 4.0, 1 H); 2.10 (*s*, 3 H); 0.99 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_3)MeCN): 167.5; 148.7; 127.1; 104.4; 79.8; 68.3; 49.5; 34.6; 25.3; 7.0. HR-ESI-MS: 239.1394 ($C_{12}H_{19}N_2O_3^+$, $[M+H]^+$; calc. 239.1390). IR (neat): 2966, 2353, 1740, 1688, 1541, 1195, 768. M.p. > 90 °C, decomposition. $[\alpha]_D^{20} = +37.4$ ($c = 0.68$, MeCN).

(3*S*)-3-*tert*-Butyl-6-(3-carboxypropyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium bromide (**L^2**). The title compound (**L^2**, 478 mg, 0.51 mmol, 64%) was obtained as an orange viscous oil following *General Procedure A* using the corresponding imidazole (**6a**, 144 mg, 0.80 mmol, 1.0 equiv.) and ethyl 4-bromobutyrate (0.17 mL, 1.20 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC ($MeOH/CH_2Cl_2$/AcOH 10:90:1, $R_f = 0.07$). ^{1}H-NMR (500 MHz, (D_3)MeCN): 10.35 (br. *s*, 1 H); 8.61 (*s*, 1 H); 5.07 (*dd*, *J* = 9.6, 8.2, 1 H); 5.00 (*dd*, *J* = 9.5, 4.1, 1 H); 4.64 (*dd*, *J* = 8.2, 4.2, 1 H); 4.21–4.09 (*m*, 2 H); 2.46 (*t*, *J* = 6.4, 2 H); 2.16 (*s*, 3 H); 2.13–2.02 (*m*, 2 H); 0.99 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_3)MeCN): 173.9; 149.2; 125.9; 103.7; 79.8; 68.1; 48.1; 34.5; 31.2; 25.6; 25.4; 7.2. HR-ESI-MS: 267.1706 ($C_{14}H_{23}N_2O_3^+$, $[M+H]^+$; calc. 267.1703). IR (neat): 3378, 2960, 2353, 1720, 1691, 1538, 1538, 1384, 1189. $[\alpha]_D^{20} = +67.5$ ($c = 0.52$, MeCN).

(3*S*)-3-*tert*-Butyl-6-(4-carboxybutyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^3**). The title compound (**L^3**, 180 mg, 0.50 mmol, 52%) was obtained as an orange viscous oil following *General Procedure A* using the corresponding imidazole (**6a**, 171 mg, 0.94 mmol, 1.0 equiv.) and methyl 5-bromovalerate (0.20 mL, 1.42 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC (silica gel, $MeOH/CH_2Cl_2$/AcOH 10:90:1, $R_f = 0.21$). ^{1}H-NMR (400 MHz, (D_3)MeCN): 9.47 (br. *s*, 1 H); 8.39 (*s*, 1 H); 5.11–5.00 (*m*, 2 H); 4.61 (*dd*, *J* = 7.9, 4.4, 1 H); 4.11–4.05 (*m*, 2 H); 2.40 (*t*, *J* = 7.2, 2 H); 2.17 (*s*, 3 H); 1.86 (*quint*, *J* = 7.3, 2 H); 1.63 (*quint*, *J* = 15.3, 7.5, 2 H); 1.01 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_3)MeCN): 174.5; 149.2; 125.6; 103.6; 79.7; 68.1; 48.6; 34.6; 33.8; 29.3; 25.4; 22.1; 7.2. HR-ESI-MS: 281.1863

($C_{15}H_{25}N_2O_3^+$, $[M-Br]^+$; calc. 281.1860). IR (neat): 3385, 2962, 1723, 1683, 1539, 1475, 1374, 1195, 633. $[\alpha]_D^{20} = +29.1$ ($c = 0.51$, MeCN).

(3*S*)-3-*tert*-Butyl-6-(5-carboxypentyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^4**). The title compound (**L^4**, 155 mg, 0.41 mmol, 50%) was obtained as an orange viscous oil following *General Procedure A* using the corresponding imidazole (**6a**, 148 mg, 0.82 mmol, 1.0 equiv.) and methyl 6-bromohexanoate (0.20 mL, 1.23 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC (silica gel, MeOH/CH_2Cl_2/AcOH 10:90:1, $R_f = 0.18$). ^{1}H-NMR (400 MHz, (D_3)MeCN): 8.49 (*s*, 1 H); 5.11–4.97 (*m*, 2 H); 4.63 (*dd*, *J* = 8.0, 4.3, 1 H); 4.13–3.99 (*m*, 2 H); 2.33 (*t*, *J* = 7.3, 2 H); 2.14 (*s*, 3 H); 1.86–1.76 (*m*, 2 H); 1.63 (*dtd*, *J* = 14.9, 7.6, 2.6, 2 H); 1.42–1.31 (*m*, 2 H); 0.99 (*s*, 9 H). ^{13}C-NMR (101 MHz, (D_3)MeCN): 174.9; 149.2; 125.6; 103.6; 79.7; 68.1; 48.7; 34.6; 34.2; 29.6; 26.0; 25.3; 24.8; 7.1. HR-ESI-MS: 295.2020 ($C_{16}H_{27}N_2O_3^+$, $[M-Br]^+$; calc. 295.2016). IR (neat): 2970, 2905, 2362, 2340, 1726, 1683, 1539, 1395, 1054, 761. $[\alpha]_D^{20} = +36.8$ ($c = 0.52$, MeCN).

(3*S*)-3-*tert*-Butyl-6-(6-carboxyhexyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^5**). The title compound (**L^5**, 123 mg, 0.31 mmol, 38%) was obtained as an orange viscous oil following *General Procedure A* using the corresponding imidazole (**6a**, 147 mg, 0.82 mmol, 1.0 equiv.) and ethyl 7-bromoheptanoate (0.24 mL, 1.22 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC (silica gel, MeOH/CH_2Cl_2/AcOH 10:90:1, $R_f = 0.16$). ^{1}H-NMR (400 MHz, (D_3)MeCN): 9.37 (br. *s*, 1 H); 8.37 (*s*, 1 H); 5.09–4.97 (*m*, 2 H); 4.60 (*dd*, *J* = 8.0, 4.3, 1 H); 4.03 (*td*, *J* = 7.1, 3.4, 2 H); 2.30 (*t*, *J* = 7.3, 2 H); 2.14 (*s*, 3 H); 1.79 (*quint*, *J* = 7.2, 2 H); 1.57 (*quint*, *J* = 7.2, 2 H); 1.42–1.30 (*m*, 4 H); 0.99 (*s*, 9 H). ^{13}C-NMR (101 MHz, (D_3)MeCN): 175.1; 149.2; 125.7; 103.5; 79.7; 68.1; 48.8; 34.5; 34.4; 29.8; 28.9; 26.2; 25.4; 25.3; 7.2. HR-ESI-MS: 309.2177 ($C_{17}H_{29}N_2O_3^+$, $[M-Br]^+$; calc. 309.2173). IR (neat): 3380, 2953, 2352, 2341, 1719, 1691, 1537, 1465, 1383, 1189, 676. $[\alpha]_D^{20} = +31.9$ ($c = 0.57$, MeCN).

Methyl 2-(Bromomethyl)benzoate (**13**). NBS (1.77g, 10.0 mmol, 1.00 equiv.) and BPO (0.04 g, 0.2 mmol, 0.02 equiv.) were added to a solution of methyl 2-methylbenzoate (1.50 g, 10.0 mmol, 1.00 equiv.) in CCl_4 (30 mL). The resulting mixture was refluxed for 5 h. After cooling down to 25 °C, the mixture was diluted with water. The phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, Et_2O/pentane 5:95, $R_f = 0.40$) affording the title compound (**13**, 2.27 g, 9.9 mmol, 99%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.99–7.94 (*m*, 1 H); 7.52–7.44 (*m*, 2 H); 7.40–7.34 (*m*, 1 H); 4.96 (*s*, 2 H); 3.94 (*s*, 3 H). ^{13}C-NMR (101 MHz, $CDCl_3$): 167.1; 139.3; 132.7; 131.8; 131.4; 129.2; 128.7; 52.4; 31.7. NMR spectra are consistent with literature data.[54]

(3*S*)-3-*tert*-Butyl-6-[(2-carboxyphenyl)methyl]-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^6**). The title compound (**L^6**, 275 mg, 0.69 mmol, 98%) was obtained as a yellow solid following *General Procedure B* using the corresponding imidazole (**6a**, 127 mg, 0.71 mmol, 1.0 equiv.) and methyl 2-(bromomethyl)benzoate (**13**, 178 mg, 0.78 mmol, 1.1 equiv.) as alkylating agent. The hydrolysis took 24 h under reflux. ^{1}H-NMR (400 MHz, (D_3)MeCN): 8.32 (*s*, 1 H); 8.11 (*dd*, *J* = 7.7, 1.5, 1 H); 7.66–7.59 (*m*, 1 H); 7.56–7.50 (*m*, 1 H); 7.15 (*dd*, *J* = 7.7, 1.2, 1 H); 5.68 (*s*, 2 H); 5.15–5.00 (*m*, 2 H); 4.65 (*dd*, *J* = 8.0, 3.9, 1 H); 2.03 (*s*, 3 H); 0.98 (*s*, 9 H). ^{13}C-NMR (101 MHz, (D_3)MeCN): 168.0; 149.3; 135.7; 134.2; 134.2; 132.8; 130.0; 130.0; 126.4; 104.3; 79.8; 68.2; 51.2; 34.6; 25.3; 7.3. HR-ESI-MS: 315.1706 ($C_{18}H_{23}N_2O_3^+$, $[M-Br]^+$; calc. 315.1703). IR (neat): 3377, 2964, 2361, 1684, 1538, 1475, 1201, 747, 647. M.p. >80 °C, decomposition. $[\alpha]_D^{20} = +29.4$ ($c = 0.46$, MeCN).

Methyl [2-(Bromomethyl)phenyl]acetate (**14**).[55] Thionyl bromide (0.35 mL, 4.55 mmol, 1.3 equiv.) was added dropwise to a stirred solution of 3-isochromanone (500 mg, 3.37 mmol, 1.0 equiv.) in dry MeOH (0.45 mL) and dry toluene (25 mL) at 25 °C under Ar. After 1 h, the mixture was carefully poured into an excess of an aqueous 20 wt-% $NaHCO_3$ solution and the resulting mixture was stirred for 10 min before it was transferred into a separating funnel. The phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The two organic layers were washed independently with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (**14**, 623 mg, 2.56 mmol, 76%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.39–7.35 (*m*, 1 H); 7.32–7.23 (*m*, 3 H); 4.59 (*s*, 2 H); 3.81 (*s*, 2 H); 3.71 (*s*, 3

H). ^{13}C-NMR (101 MHz, $CDCl_3$): 171.6; 136.5; 133.4; 131.4; 130.8; 129.3; 128.2; 52.4; 38.3; 31.9.

(3*S*)-3-*tert*-Butyl-6-{[2-(2-methoxy-2-oxoethyl) phenyl]methyl}-7-methyl-3,6-dihydro-2*H*-imidazo-[5,1-*b*][1,3]oxazol-4-ium Bromide (**15**). The title compound (**15**, 252 mg, 0.62 mmol, 99%) was obtained as a yellow solid following the first part of *General Procedure B* using the corresponding imidazole (**6a**, 106 mg, 0.59 mmol, 1.0 equiv.) and methyl [2-(bromomethyl)phenyl]acetate (**14**, 80% purity, 185 mg, 0.65 mmol, 1.1 equiv.) as alkylating agent. ^{1}H-NMR: (400 MHz, $CDCl_3$): 9.90 (*s*, 1 H); 7.36–7.22 (*m*, 3 H); 6.95–6.87 (*m*, 1 H); 5.78–5.63 (*m*, 2 H); 5.20–5.11 (*m*, 1 H); 4.97–4.89 (*m*, 2 H); 3.86–3.76 (*m*, 2 H); 3.67 (*s*, 3 H); 2.01 (*s*, 3 H); 1.07 (*s*, 9 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 171.5; 148.4; 132.4; 132.3; 131.8; 129.2; 128.6; 127.8; 127.1; 102.9; 78.7; 67.5; 52.5; 49.9; 38.8; 34.0; 25.6; 7.3. HR-ESI-MS: 343.2022 ($C_{20}H_{27}N_2O_3^+$, $[M-Br]^+$; calc. 343.2016). IR (neat): 2962, 2361, 2341, 1733, 1682, 1539, 1457, 1197, 168, 630. M.p. 48 °C. $[\alpha]_D^{20} = +37.0$ ($c = 0.57$, $CHCl_3$).

(3*S*)-3-*tert*-Butyl-6-{[2-(carboxymethyl)phenyl] methyl}-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^7**). The title compound (**L^7**, 672 mg, 1.64 mmol, 99%) was obtained as a yellow solid following *General Procedure B* using the corresponding imidazole (**6a**, 295 mg, 1.64 mmol, 1.0 equiv.) and methyl [2-(bromomethyl)phenyl] acetate (**14**, 80% purity, 548 mg, 1.80 mmol, 1.1 equiv.) as alkylating agent. The hydrolysis took 2 h under reflux. ^{1}H-NMR (500 MHz, (D_3)MeCN): 8.34 (*s*, 1 H); 7.45–7.27 (*m*, 3 H); 7.10–6.99 (*m*, 1 H); 5.44–5.27 (*m*, 2 H); 5.13 (*dd*, $J = 9.5$, 8.2, 1 H); 5.03 (*dd*, $J = 9.6$, 4.0, 1 H); 4.68 (*dd*, $J = 8.2$, 4.0, 1 H); 3.89–3.76 (*m*, 2 H); 2.03 (*s*, 3 H); 0.99 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_3)MeCN): 172.4; 149.4; 134.8; 133.0; 132.8; 130.1; 129.1; 129.0; 126.3; 104.3; 79.9; 68.3; 50.4; 39.2; 34.5; 25.3; 7.4. HR-ESI-MS: 329.1865 ($C_{19}H_{25}N_2O_3^+$, $[M-Br]^+$; calc. 329.1860). IR (neat): 2963, 2924, 2361, 2340, 1720, 1684, 15399, 1457, 1373, 1196, 781, 630. M.p. > 120 °C decomposition. $[\alpha]_D^{20} = +52.4$ ($c = 0.54$, $CHCl_3$).

Methyl 3-[2-(Bromomethyl)phenyl]propanoate (**16**). *m*-Chloroperbenzoic acid (70% purity, 3.37 g, 13.7 mmol, 2.0 equiv.) was added to a solution of β-tetralone (1.00 g, 6.8 mmol, 1.0 equiv.) in dry CH_2Cl_2 (14 mL) under Ar. The resulting mixture was stirred at 25 °C for 16 h. The precipitate was filtered off and the filtrate was washed with sat. Na_2SO_3 solution, followed by sat. $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained white solid was dissolved in dry toluene (20 mL) and dry MeOH (0.45 mL) under Ar. Thionyl bromide (0.35 mL, 0.7 equiv.) was added dropwise. After 1 h of stirring at 25 °C, the mixture was carefully poured into an excess of an aqueous 20 wt-% $NaHCO_3$ solution, and the resulting mixture was stirred for 10 min before it was transferred into a separating funnel. The phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The two organic layers were washed independently with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, Et_2O/cyclohexane 1:9) to afford a mixture of the title compound (**16**) and its regioisomer (82:18, 500 mg, 1.94 mmol, 28%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 (*dd*, $J = 7.8$, 1.6, 1 H); 7.30–7.23 (*m*, 1 H); 7.23–7.18 (*m*, 2 H); 4.58 (*s*, 2 H); 3.70 (*s*, 3 H); 3.08 (*dd*, $J = 8.7$, 7.1, 2 H); 2.76–2.67 (*m*, 2 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 173.3, 139.6, 135.8, 130.9, 129.6, 129.4, 127.2, 51.9, 34.9, 31.6, 27.3.

Data of the Regioisomer **Methyl [2-(2-bromoethyl) phenyl]acetate**: ^{1}H-NMR (500 MHz, $CDCl_3$): 7.29–7.24 (*m*, 4 H); 3.70 (*s*, 3 H); 3.69 (*s*, 2 H); 3.54 (*dd*, $J = 8.5$, 7.4, 2 H); 3.21 (*dd*, $J = 8.4$, 7.4, 2 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 173.3; 139.6; 135.8; 130.9; 129.6; 129.4; 127.2; 51.9; 34.9; 31.6; 27.3.

(3*S*)-3-*tert*-Butyl-6-{[2-(2-carboxyethyl)phenyl] methyl}-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^8**). The title compound (**L^8**, 111 mg, 0.25 mmol, 68%) was obtained as an orange solid following *General Procedure B* using the corresponding imidazole (**6a**, 67 mg, 0.37 mmol, 1.0 equiv.) and methyl 3-[2-(bromomethyl)phenyl] propanoate (**16**; 82% purity, 163 mg, 0.52 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 2 h under reflux. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.33 (*s*, 1 H); 7.35–7.27 (*m*, 2 H); 7.27–7.19 (*m*, 1 H); 6.90 (*d*, $J = 7.7$, 1 H); 5.68–5.54 (*m*, 2 H); 5.20 (*t*, $J = 8.7$, 1 H); 5.06 (*dd*, $J = 8.1$, 3.6, 1 H); 4.91 (*dd*, $J = 9.3$, 3.5, 1 H); 3.00 (*t*, $J = 7.4$, 2 H); 2.70 (*ddt*, $J = 48.4$, 15.3, 7.4, 2 H); 2.06 (*s*, 3 H); 1.05 (*s*, 9 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 174.5; 148.6; 139.3; 130.8; 130.6; 129.6; 127.7; 127.5; 126.9; 103.1; 78.9; 67.5; 50.2; 36.1; 34.0; 27.8; 25.6; 7.6. HR-ESI-MS: 343.2023 ($C_{20}H_{27}N_2O_3^+$, $[M-Br]^+$; calc. 343.2016). IR (neat): 3385, 2963, 2923, 2361, 2341, 1724, 1682, 1538, 1454, 1374, 1195, 760, 630. M.p. 96 °C. $[\alpha]_D^{20} = +27.5$ ($c = 0.53$, $CHCl_3$).

Methyl 2,2-Dimethyl-3-[(trifluoromethanesulfonyl)oxy]propanoate (**17**). Tf_2O (1.65 mL, 9.84 mmol, 1.3 equiv.) was added dropwise to a solution of methyl hydroxypivalate (1.00 g, 7.57 mmol, 1.0 equiv.) and 2,6-lutidine (1.32 mL, 11.4 mmol, 1.5 equiv.) in dry CH_2Cl_2 (21 mL) at −78 °C under Ar. The mixture was stirred for 3 h at the same temperature before it was allowed to warm to 25 °C. The reaction was quenched by addition of sat. NH_4Cl. The two phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, AcOEt/petroleum ether 3:7, R_f = 0.85) to afford the title compound (**17**, 1.47 g, 5.58 mmol, 73%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.50 (*s*, 2 H); 3.74 (*s*, 3 H); 1.30 (*s*, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$): 174.3; 118.8 (*q*, *J* = 319.7); 81.1; 52.7; 43.2; 21.9. ^{19}F-NMR (471 MHz, $CDCl_3$): −74.5.

(3*S*)-3-*tert*-Butyl-6-(3-methoxy-2,2-dimethyl-3-oxopropyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Trifluoromethanesulfonate (**18**). Methyl 2,2-dimethyl-3-[(trifluoromethanesulfonyl)oxy]propanoate (**17**, 220 mg, 0.83 mmol, 1.5 equiv.) was added to (3*S*)-3-*tert*-butyl-7-methyl-2,3-dihydroimidazo[5,1-*b*][1,3]oxazole (**6a**, 100 mg, 0.56 mmol, 1.0 equiv.) in dry MeCN (1.5 mL) under Ar. The mixture was stirred at 70 °C for 16 h. The solvent was removed under reduced pressure. A minimal amount of CH_2Cl_2 was added to dissolve the crude mixture, and Et_2O was added to precipitate the product. The solvent was removed, and the residue further dried to afford the title compound (**18**, 157 mg, 0.35 mmol, 63%) as an orange viscous oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.65 (*s*, 1 H); 5.12 (*dd*, *J* = 9.3, 8.1, 1 H); 4.92 (*dd*, *J* = 9.3, 3.3, 1 H); 4.80 (*dd*, *J* = 8.1, 3.4, 1 H); 4.32 (*d*, *J* = 14.6, 1 H); 4.17 (*d*, *J* = 14.6, 1 H); 3.75 (*s*, 3 H); 2.16 (*s*, 3 H); 1.33 (*s*, 3 H); 1.29 (*s*, 3 H); 1.03 (*s*, 9 H). ^{13}C-NMR (101 MHz, $CDCl_3$): 175.5; 148.2; 127.5; 103.1; 78.7; 67.4; 54.6; 53.0; 44.3; 34.1; 25.4; 23.5; 23.3; 7.6. ^{19}F-NMR (376 MHz, $CDCl_3$): −78.5. HR-ESI-MS: 295.2020 ($C_{16}H_{27}N_2O_3^+$, $[M-OTf]^+$; calc. 295.2016). IR (neat): 2972, 2361, 2340, 1731, 1539, 1477, 1278, 1159, 1031, 642. $[\alpha]_D^{20}$ = +16.9 (*c* = 0.97, $CHCl_3$).

(3*S*)-3-*tert*-Butyl-6-(2-carboxy-2-methylpropyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium Iodide (**L^9**). NaI (416 mg, 2.78 mmol, 5 equiv.) was added to a solution of (3*S*)-3-*tert*-butyl-6-(3-methoxy-2,2-dimethyl-3-oxopropyl)-7-methyl-3,6-dihydro-2*H*-imidazo[5,1-*b*][1,3]oxazol-4-ium trifluoromethanesulfonate (**18**, 157 mg, 0.35 mmol, 1 equiv.) in acetone (3 mL). The resulting mixture was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure and the crude filtered over a plug of *Celite* (eluent CH_2Cl_2). The solvent was evaporated and H_2O (1 mL) was added. Two drops of HI (57 wt-% in H_2O, cat.) were added to the mixture. The resulting mixture was refluxed for 48 h. After cooling down to 25 °C, the water was removed under reduced pressure. The crude mixture was purified by FC (silica gel, MeOH/CH_2Cl_2/AcOH 10:90:1, R_f = 0.16) to afford the title compound (**L^9**, 144 mg, 0.35 mmol, 98%) as an orange viscous oil. ^{1}H-NMR (400 MHz, (D_3)MeCN): 8.32 (*s*, 1 H); 5.09–4.99 (*m*, 2 H); 4.62 (*dd*, *J* = 7.6, 4.2, 1 H); 4.30–4.13 (*m*, 2 H); 2.15 (*s*, 3 H); 1.26 (*s*, 3 H); 1.25 (*s*, 3 H); 0.98 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_3)MeCN): 176.9; 149.0; 126.7; 104.6; 79.8; 68.3; 54.9; 44.7; 34.7; 25.4; 23.4; 23.3; 7.8. HR-ESI-MS: 281.1863 ($C_{15}H_{25}N_2O_3^+$; $[M-I]^+$; calc. 281.1860). IR (neat): 3703, 2960, 2923, 2853, 2361, 2340, 765, 630. $[\alpha]_D^{20}$ = +13.4 (*c* = 0.37, $CHCl_3$).

(3*S*)-3-*tert*-Butyl-6-{[2-(carboxymethyl)phenyl]methyl}-7-(propan-2-yl)-3,6-dihydro-2*H*-imidazo-[5,1-*b*][1,3]oxazol-4-ium Bromide (**L^{10}**). Methyl [2-(bromomethyl)phenyl]acetate (**14**, 193 mg, 0.79 mmol, 1.1 equiv.) was added to a solution of (3*S*)-3-*tert*-butyl-7-(propan-2-yl)-2,3-dihydroimidazo[5,1-*b*][1,3]oxazole (**6b**, 150 mg, 0.72 mmol, 1.0 equiv.) in dry acetonitrile (2 mL) under Ar. The mixture was stirred at 70 °C for 48 h. The solvent was removed under reduced pressure. A minimal amount of CH_2Cl_2 was added to dissolve the crude mixture, and Et_2O was added to precipitate the product. The solvent was removed and the residue further dried. Then, H_2O (0.1 M imidazolium solution), and two drops of HBr (48 wt-% in H_2O, cat) were added to the crude mixture, and the mixture was refluxed for 36 h. The mixture was allowed to cool down to 25 °C, and the water was removed under reduced pressure. The crude mixture was purified by FC (MeOH/CH_2Cl_2/AcOH 10:90:1, R_f = 0.08) to obtain the title compound (**L^{10}**, 138 mg, 0.31 mmol, 44%) as a yellow viscous oil. ^{1}H-NMR (400 MHz, (D_4)MeOH): 8.64 (*s*, 1 H); 7.40–7.37 (*m*, 2 H); 7.37–7.31 (*m*, 1 H); 6.97 (*d*, *J* = 7.4, 1 H); 5.50 (*s*, 2 H); 5.16 (*d*, *J* = 6.0, 2 H); 4.71 (*t*, *J* = 6.1, 1 H); 3.76 (*s*, 2 H); 2.91 (*sept*, *J* = 6.8, 1 H); 1.20 (*d*, *J* = 6.9, 3 H); 1.18 (*d*, *J* = 6.9, 3 H); 1.04 (*s*, 9 H). ^{13}C-NMR (126 MHz, (D_4)MeOH): 175.1 149.3; 135.4; 133.9; 132.9; 130.3; 129.1; 128.4; 126.9; 114.5; 114.5; 80.2; 68.6; 50.7; 34.9; 25.4; 24.6; 21.7; 21.1. HR-ESI-MS: 357.2176 ($C_{21}H_{29}N_2O_3^+$, $[M-Br]^+$; calc. 357.2173). IR

(neat): 3388, 2968, 2361, 2340, 1602, 1539, 1373, 722. $[\alpha]_D^{20} = +29.4$ ($c = 0.47$, MeOH).

Complex C[1]. The title compound (**C[1]**, 72.2 mg, 0.13 mmol, 71%) was obtained as a beige solid following *General Procedure D* using **L[1]** (60 mg, 0.19 mmol, 1.0 equiv.), and Ag_2O (43.6 mg, 0.19 mmol, 1.0 equiv.) in dry CH_2Cl_2 (18 mL) followed by Pd-dimer (63.6 mg, 0.09 mmol, 0.5 equiv.) in dry THF (5 mL). Single crystals suitable for X-ray characterization were obtained by recrystallization from a mixture of CH_2Cl_2 and hexane by solvent layering and slow diffusion. ^{1}H-NMR (500 MHz, CD_2Cl_2): 7.55–7.50 (*m*, 1 H); 7.35 (*dd*, $J = 7.7$, 1.3, 1 H); 7.31–7.24 (*m*, 3 H); 7.10 (*td*, $J = 7.3$, 1.6, 1 H); 6.91–6.83 (*m*, 2 H); 4.71 (*d*, $J = 15.5$, 1 H); 4.59 (*dd*, $J = 9.1$, 1.2, 1 H); 4.47 (*dd*, $J = 9.1$, 6.9, 1 H); 4.37 (*d*, $J = 15.6$, 1 H); 3.12 (*dd*, $J = 6.9$, 1.2, 1 H); 3.02 (*s*, 3 H); 2.57 (*s*, 3 H); 2.09 (*s*, 3 H); 0.68 (*s*, 9 H). ^{13}C-NMR (126 MHz, CD_2Cl_2): 170.7; 156.2; 151.8; 148.2; 148.1; 142.5; 141.7; 139.2; 130.7; 128.0; 126.7; 126.4; 126.2; 125.5; 117.7; 100.6; 77.7; 66.7; 53.2; 52.2; 48.4; 34.7; 26.9; 8.2. HR-ESI-MS: 1079.2872 ($C_{52}H_{63}N_6O_6Pd_2^+$, $[M+H]^+$; calc. 1079.2876). IR (neat): 2961, 2924, 2361, 2340, 1711, 1617, 1468, 1393, 1256, 1058, 633, 604. M.p. >120 °C, decomposition. $[\alpha]_D^{20} = +101.7$ ($c = 0.77$, CH_2Cl_2). Structure characterized by X-ray analysis, see Supporting Information.

Complex C[2]. The title compound (**C[2]**, 115 mg, 0.20 mmol, 97%) was obtained as a beige solid following *General Procedure D* using **L[9]** (83.0 mg, 0.20 mmol, 1.0 equiv.), and Ag_2O (47.0 mg, 0.20 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL) followed by Pd-dimer (68.6 mg, 0.10 mmol, 0.5 equiv.) in dry THF (10 mL). ^{1}H-NMR (500 MHz, CD_2Cl_2): 7.53 (*dd*, $J = 7.7$, 1.7, 1 H); 7.33 (*dd*, $J = 7.6$, 1.5, 1 H); 7.31–7.23 (*m*, 3 H); 7.13–7.04 (*m*, 1 H); 6.82 (*td*, $J = 7.4$, 1.5, 1 H); 6.45 (*d*, $J = 7.5$, 1 H); 5.31 (*d*, $J = 13.8$, 1 H); 4.54 (*dd*, $J = 9.1$, 1.5, 1 H); 4.31 (*dd*, $J = 9.1$, 7.2, 1 H); 3.66–3.62 (*m*, 1 H); 2.84–2.79 (*m*, 1 H); 2.62 (*s*, 3 H); 2.12 (*s*, 3 H); 1.41 (*s*, 3 H); 1.30 (*s*, 3 H); 1.06 (*s*, 3 H); 0.70 (*s*, 9 H). ^{13}C-NMR (126 MHz, CD_2Cl_2): 182.3; 157.9; 150.4; 148.5; 148.3; 142.5; 141.6; 138.8; 130.4; 128.1; 126.7; 126.4; 126.0; 125.4; 117.8; 101.4; 77.8; 66.0; 58.0; 52.3; 48.7; 34.7; 30.7; 27.0; 26.7; 24.2; 8.7. HR-ESI-MS: 582.1952 ($C_{29}H_{38}N_3O_3Pd^+$, $[M+H]^+$; calc. 582.1954). IR (neat): 3678, 2964, 2923, 2361, 2341, 1591, 1559, 1462, 1393, 1258, 1058, 736. M.p. >80 °C, decomposition. $[\alpha]_D^{20} = +84.0$ ($c = 0.78$, CH_2Cl_2).

Complex C[3]. The title compound (**C[3]**, 57.0 mg, 0.09 mmol, 73%) was obtained as a beige solid following *General Procedure D* using **L[6]** (50.0 mg, 0.13 mmol, 1.0 equiv.), and Ag_2O (29.2 mg, 0.13 mmol, 1.0 equiv.) in dry CH_2Cl_2 (12 mL) followed by Pd-dimer (42.6 mg, 0.06 mmol, 0.5 equiv.) in dry THF (6 mL). Single crystals suitable for X-ray characterization were obtained by slow evaporation of solvent form a THF/hexane mixture. ^{1}H-NMR (500 MHz, CD_2Cl_2): 7.57–7.51 (*m*, 2 H); 7.41–7.38 (*m*, 1 H); 7.35–7.26 (*m*, 6 H); 7.05 (*t*, $J = 7.5$, 1 H); 6.79 (*t*, $J = 7.3$, 1 H); 6.51 (*d*, $J = 14.1$, 1 H); 6.41 (*d*, $J = 7.5$, 1 H); 4.90 (*d*, $J = 14.1$, 1 H); 4.49 (*d*, $J = 9.0$, 1 H); 4.22 (*t*, $J = 8.1$, 1 H); 3.05 (*s*, 3 H); 2.88 (*d*, $J = 7.0$, 1 H); 2.55 (*s*, 3 H); 2.03 (*s*, 3 H); 0.76 (*s*, 9 H). ^{13}C-NMR: due to some impurities and overlapping of some signals, the ^{13}C signals could not be assigned to the structure. HR-ESI-MS: 616.1799 ($C_{32}H_{36}N_3O_3Pd^+$, $[M+H]^+$; calc. 616.1798). IR (neat): 2957, 2925, 2854, 2362, 2339, 1705, 1605, 1563, 1438, 1382, 1257, 942, 739. M.p. >110 °C decomposition. $[\alpha]_D^{20} = -29.5$ ($c = 0.42$, CH_2Cl_2). Structure characterized by X-ray analysis, see Supporting Information.

Complex C[4]. The title compound (**C[4]**, 35.2 mg, 0.056 mmol, 89%) was obtained as an off-white solid following *General Procedure D* using **L[7]** (25.7 mg, 0.063 mmol, 1.0 equiv.), Ag_2O (14.6 mg, 0.063 mmol, 1.0 equiv.) in dry CH_2Cl_2 (7 mL), followed by Pd-dimer (21.2 mg, 0.032 mmol, 0.5 equiv.) in dry THF (3.5 mL). ^{1}H-NMR: (500 MHz, CD_2Cl_2): 7.57–7.51 (*m*, 1 H); 7.44 (*dd*, $J = 7.2$, 2.0, 1 H); 7.39–7.31 (*m*, 3 H); 7.30–7.19 (*m*, 3 H); 7.15 (*dd*, $J = 7.9$, 1.5, 1 H); 7.01–6.96 (*m*, 1 H); 6.80–6.74 (*m*, 1 H); 6.19 (*d*, $J = 7.5$, 1 H); 5.38 (*d*, $J = 14.4$, 1 H); 5.02 (*d*, $J = 14.2$, 1 H); 4.47 (*d*, $J = 9.0$, 1 H); 4.10 (*t*, $J = 8.0$, 1 H); 3.78–3.60 (*m*, 2 H); 2.78 (*d*, $J = 6.1$, 1 H); 2.74 (*s*, 3 H); 2.19 (*s*, 3 H); 2.15 (*s*, 3 H); 0.73 (*s*, 9 H). ^{13}C-NMR (126 MHz, CD_2Cl_2): 176.0; 157.7; 149.0; 148.7; 148.5; 142.4; 141.6; 139.1; 138.3; 135.9; 132.1; 131.9; 130.3; 129.1; 128.1; 127.3; 126.4; 126.2; 125.5; 125.1; 117.6; 102.2; 78.2; 66.2; 51.3; 50.3; 48.2; 44.1; 34.5; 26.4; 8.8. HR-ESI-MS: 630.1956 ($C_{33}H_{38}N_3O_3Pd^+$, $[M+H]^+$; calc. 630.1955). IR (neat): 2960, 2924, 2362, 2340, 1716, 1592, 1391, 1058, 783. M.p. >90 °C, decomposition. $[\alpha]_D^{20} = -50.1$ ($c = 0.61$, CH_2Cl_2).

Methyl 2-methyl-2,3-dihydro-1*H*-indole-1-carboxylate (**8**). The title compound **8** was obtained following *General Procedure E* using aryl bromide (**7**, 13.6 mg, 0.050 mmol, 1 equiv.), Cs_2CO_3 (24.7 mg, 0.075 mmol, 1.5 equiv.), **C[4]** (3.2 mg, 0.005 mmol, 0.1 equiv.), and HFIP (1 μL, 0.01 mmol, 0.2 equiv.) in mesitylene (0.5 mL). The crude mixture was purified by FC (silica gel, Et_2O/petroleum ether 8:92, $R_f = 0.28$) affording a light yellow oil. ^{1}H-NMR yield: 20%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 (br. *s*, 1 H); 7.23–7.12 (*m*, 2

H); 6.97 (*t*, *J* = 7.4, 1 H); 4.62–4.48 (*m*, 1 H); 3.85 (*s*, 3 H); 3.36 (*dd*, *J* = 15.9, 9.5, 1 H); 2.63 (*dd*, *J* = 15.9, 2.4, 1 H); 1.30 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR (126 MHz, $CDCl_3$): 153.7; 141.6; 130.1; 127.6; 125.1; 122.8; 115.5; 55.5; 52.5; 36.0; 21.3. HPLC separation: *Chiralcel OJ-H*; hexane/^{i}PrOH 99:1, 1 mL/min, 243 nm, t_r(minor) = 9.7 min, t_r(major) = 10.7 min, 22:78 e.r. All analytical data are consistent with literature data.[19] Racemic **8** was synthesized according to literature from **7**.[19]

Supplementary Material

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.2100015. CCDC-2056907 (**C^1**) and CCDC-2056906 (**C^3**) contain(s) the supplementary crystallographic data for this work. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre through https://www.ccdc.cam.ac.uk/structures/.

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Author Contribution Statement

N. E. N. designed and performed the experiments and wrote the draft manuscript. *O. B.* supervised the work and wrote the manuscript together with *N. E. N.*

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