Enantioselective Synthesis of *N*-Benzylic Heterocycles: a Nickel- and Photoredox-Dual Catalysis Approach.

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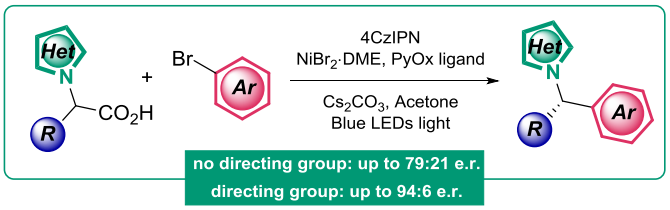
Supporting Information Placeholder



ABSTRACT: Reported herein is a dual nickel- and photoredox-catalysed modular approach for the preparation of enantioenriched *N*-benzylic heterocycles. α-Heterocyclic carboxylic acids, easily obtainable from common commercial material, are reported as suitable substrates for a decarboxylative strategy in conjunction with a chiral pyridine-oxazoline (PyOx) ligand, providing quick access to enantioenriched drug-like products. The presence of a directing group on the heterocyclic moiety is shown to be beneficial, affording improved stereoselectivity in a number of cases.

N-Benzylic heterocycles constitute an important class of heterocyclic compounds in the pharmaceutical industry, with numerous examples of commercial drugs and bioactive molecules.[1] A subset of these molecules contain chirality at the α-position of the benzylic moiety (Figure 1), with important effects on their pharmacological properties. For example, the anaesthetic drug etomidate contains an imidazole ring with a chiral *N*-benzylic substituent;[2] the anaesthetic potency is one order of magnitude higher for the (*R*) enantiomer compared to the (*S*) enantiomer.[3] Their preparation typically involves the synthesis of the heterocycle from a chiral benzylic amine,[4,5] or the nucleophilic substitution of a suitable chiral precursor with the nitrogen heterocycle.[6] While these methods can be effective, the lack of modularity hampers quick access to different structures, necessitating the preparation of an enantiopure precursor for every desired entry. Moreover, substitution using heterocycles with multiple nitrogen atoms can lead to the formation of isomers,[7] resulting in low yields and difficulty of separation while consuming such precious chiral precursors. A modular approach, allowing the use of prochiral and easily obtainable substrates, is thus desirable.

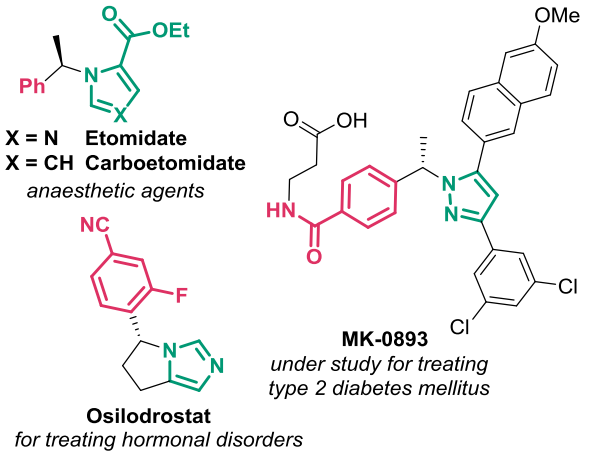


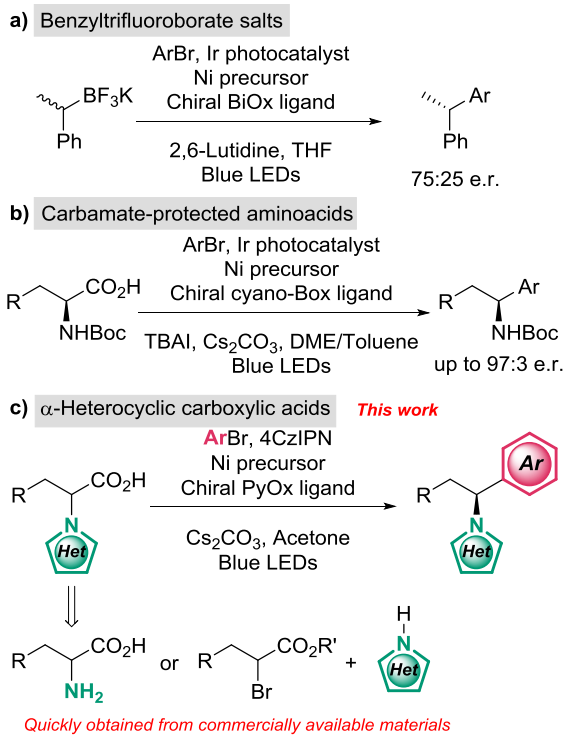
Figure 1. Examples of pharmaceutically-relevant compounds bearing a chiral N-benzylic heterocycle motif.

Photoredox catalysis is certainly one of the most interesting and active fields of research of the moment.[8] Upon visible light irradiation, reactive radical species can be generated in exceptionally mild conditions. Moreover, recent efforts in coupling this mode of activation with nickel catalysis have further enlarged the scope of the field.[9] Efficient cross-coupling reactions can be obtained between aryl halides and a variety of radical sources: relevant examples include carboxylates,[10] alkyltrifluoroborates[11] and alkyldihydropyridines.[12] Even simple C–H bonds, within proper hydrogen atom transfer (HAT) manifolds,

can engage into Ni–radical cross-couplings.[13] While it is possible to generate prochiral secondary alkyl radicals from such precursors, the field of enantioselective Ni–photoredox cross-couplings is still under-explored.[14] In 2014, the Molander group described the first example of the use of alkyltrifluoroborate salts in Ni–photoredox cross-couplings, showing that stereocontrol can be obtained with a chiral bioxazoline as ligand (Scheme 1a).[11a] Starting from carboxylate salts, the MacMillan and Fu groups demonstrated how the use of a chiral cyano-bis-oxazoline ligand was effective in catalysing an enantioselective decarboxylative cross-coupling with carbamate-protected aminoacids (Scheme 1b).[10d] During the preparation of this manuscript, Lu's group also reported an efficient asymmetric cross-coupling leading to 1,1-diarylalkanes, with a chiral biimidazoline as ligand.[15] Similar systems were used by other groups in isolated examples of enantioselective cross-coupling reactions.[11d,13e,16]

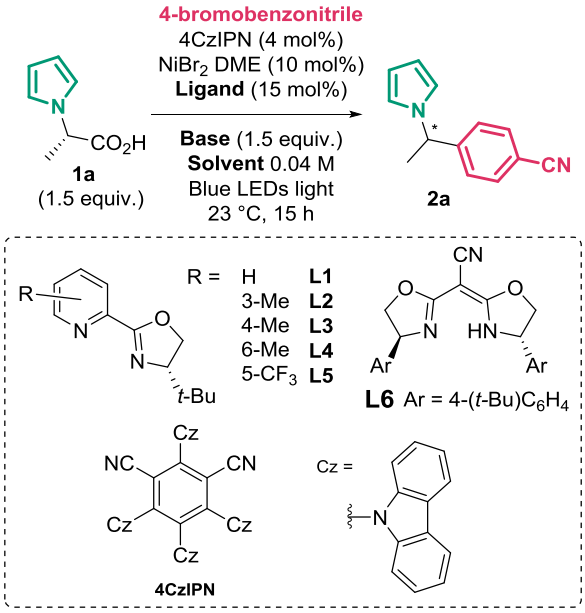
Here we report a Ni–photoredox cross-coupling-based approach for the preparation of chiral *N*-benzylic heterocycles (Scheme 1c), which have been rarely considered within these catalytic manifolds.[17] α-Heterocyclic carboxylic acids have been successfully coupled with aryl bromides, while the introduction of a pyridine-oxazoline (PyOx) chiral ligand allowed sterocontrol in such C–C bond-forming reaction where previous conditions failed.[10d] We also found the presence of a directing handle on the heterocyclic moiety to be important for improving stereoselectivity. Chiral, drug-like compounds could thus be prepared in a simple, modular fashion from easily obtainable materials.

Scheme 1. Enantioselective Ni-photoredox cross-couplings and approach to the synthesis of *N*-benzylic heterocycles.



Our investigation started with an evaluation of ligands for the conversion of pyrrole carboxylic acid **1a** (prepared from L-alanine) and 4-bromobenzonitrile into chiral benzylic pyrrole **2a**. The reaction was conducted using DMF as solvent, 4CzIPN as photocatalyst,[18] $NiCl_2$·DME as nickel source and Cs_2CO_3 as base under blue light irradiation (λ_{irr} = 450-455 nm). Among the different nitrogen- and phosphorous-containing ligands examined (see ESI, Table S1), pyridine-oxazoline (PyOx)[19] ligand **L1** emerged as effective and versatile, providing 50% yield and 69:31 e.r. (Table 1, entry 1). During our optimisation work we observed that cyano-bis-oxazoline **L6** and related ligands are also competent catalysts, affording satisfactory levels of enantioselectivity (22:78 e.r., entry 2). However, they show reduced reactivity and extremely narrow scope, which prompted us to exclude them from further analysis (see ESI).

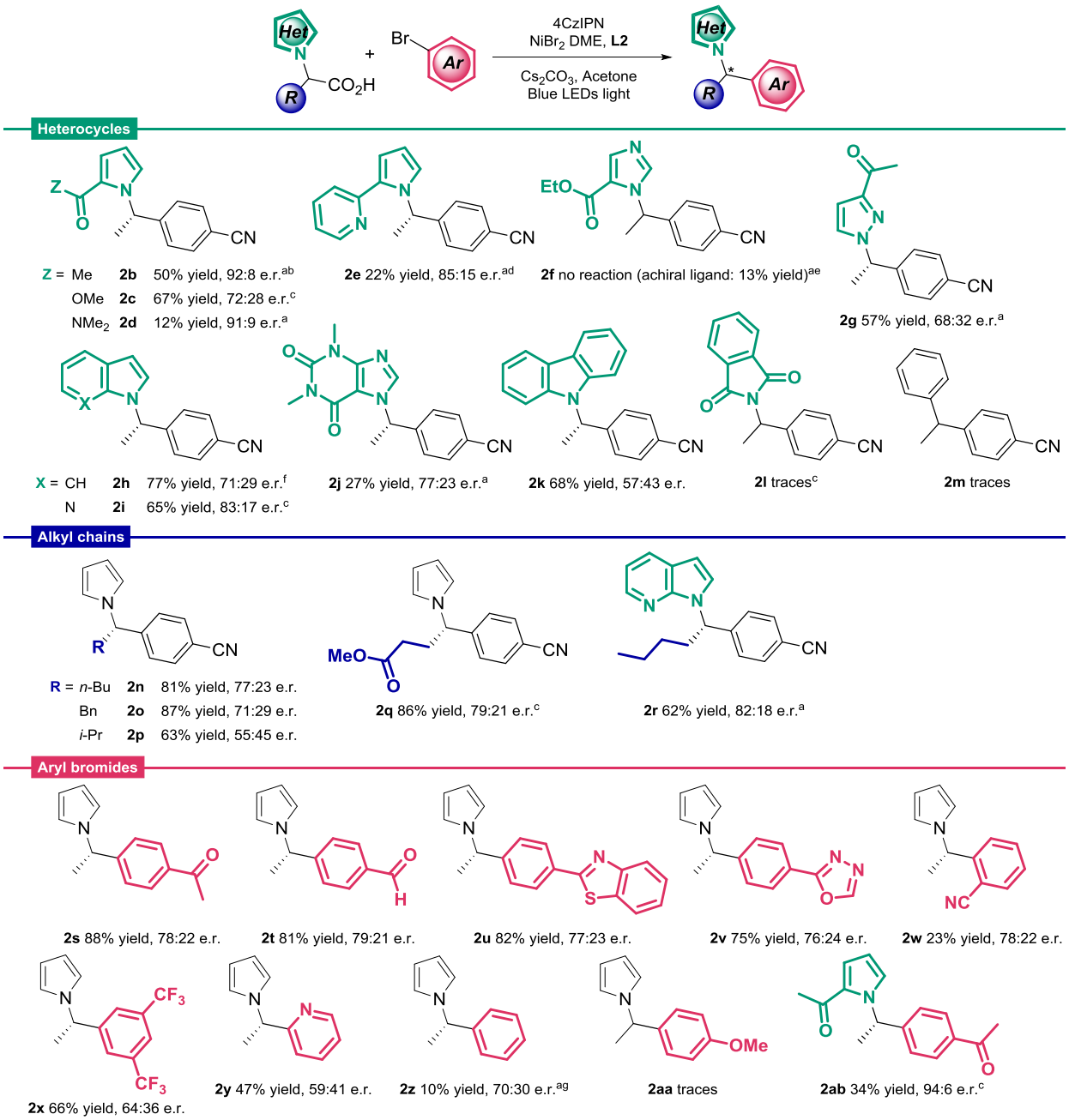
Table 1. Optimisation: selection of results.[a]



Entry	Ligand	Base	Solvent	Yield (%)[b]	e.r.[b]
1[c]	L1	Cs_2CO_3	DMF	50	69:31
2[c]	L6	Cs_2CO_3	DME	56	22:78
3	L1	Cs_2CO_3	DMF	58	69:31
4	L1	Cs_2CO_3	ACN	62	73:27
5	L1	Cs_2CO_3	Acetone	75	73:27
6	L2	Cs_2CO_3	Acetone	90 (80)	77:23
7	L3	Cs_2CO_3	Acetone	74	72:28
8	L4	Cs_2CO_3	Acetone	9	51:49
9	L5	Cs_2CO_3	Acetone	15	50:50
10	L2	CsOH·H_2O	Acetone	87	76:24
11	L2	DBU	Acetone	88	77:23
12[d]	L2	Cs_2CO_3	Acetone	91	76:24
13[e]	L2	Cs_2CO_3	Acetone	84	76:24
14[f]	L2	Cs_2CO_3	Acetone	86	76:24
15[g]	L2	Cs_2CO_3	Acetone	(89)	77:23

[a] For further details on optimisation experiments, see ESI. [b] Yield and e.r. determined by SFC analysis of reaction mixtures with an external standard. Isolated yield in parentheses. [c] Experiment run with $NiCl_2$·DME (10 mol%). [d] Experiment run with 10 mol% of ligand. [e] Experiment run with 5 mol% of $NiBr_2$·DME and 7.5 mol% of ligand. [f] Experiment run with enantiomer of substrate, derived from D-alanine. [g] Performed on a 1 mmol scale, see SI for details. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine.

Scheme 2. Substrate scope.



Isolated yields reported. Standard conditions as in Table 1, entry 6, with 11 mol% **L2**. Notes: [a] Reaction time: 64 h. [b] 8 mol% 4CzIPN used. [c] Reaction time: 40 h. [d] 1.1 equiv. of carboxylic acid and Cs_2CO_3 were used. [e] ^{1}H-NMR yield of racemic product. Experiment run in DMF with $NiCl_2$·DME (10 mol%), dtbbpy (15 mol%), $Ir(dF(CF_3)_2bpy)_2(dtbbpy)PF_6$ (2 mol%), 1 equiv. of imidazolic acid and Cs_2CO_3. Our standard conditions failed to deliver any product. [f] Experiment run with **L1** as ligand. Reaction with **L2** affords product in 97% chromatographic yield and 57:43 e.r.. [g] ^{1}H-NMR yield: 20%.

Subsequent optimization experiments showed improvements in using $NiBr_2$·DME as Ni source (entry 3) and acetone as solvent (entries 4-5). With a better set of conditions in hand, an evaluation of structurally modified PyOx ligands was performed (entries 6-9). The introduction of a methyl group in the C3 position of the pyridine ring (ligand **L2**) proved highly beneficial in terms of reactivity (90% yield, entry 6), while also providing a small improvement in enantioselectivity (77:23 e.r.). It was subsequently found that **L2** provides a much more active catalytic system: full conversion to **2a** was obtained in 4 h instead of 15 h when compared to **L1** and **L6** (Figure 2). Moving the methyl to the C4 position (ligand **L3**) provided the same results as **L1** (entry 7). Introducing a methyl group in C6 position (ligand **L4**) or an electron-withdrawing trifluoromethyl group in C5 position (ligand **L5**) proved to be deleterious (entries 8-9). Having selected **L2** as the most promising ligand for this transformation, a final screen of bases revealed that only $CsOH·H_2O$ (entry 10) and DBU (entry 11) provided product with the same efficiency as Cs_2CO_3. Finally, reducing the ligand:Ni ratio to 1:1 provided the same results as the initial 1.5:1 ratio (entry 12), while reducing the loading of the Ni catalyst

from 10 to 5% afforded a slightly reduced 84% yield (entry 13). If the enantiomer of the substrate, derived from D-alanine, is employed the same enantiomer of the product is obtained with the same stereoselectivity (entry 14), confirming the enantioconvergent nature of the process. The effect of temperature was also evaluated, but minimal differences in enantioselectivity were observed between 0 °C and 35 °C (see ESI, Table S9). Control experiments confirmed the necessity of all the reaction elements to the success of the transformation (see ESI, Table S8). Pleasingly, the reaction can be successfully scaled up from 0.2 mmol to a more synthetically useful 1.0 mmol scale, affording **2a** in 89% yield and 77:23 e.r., with no loss in reactivity or enantioselectivity (entry 15).

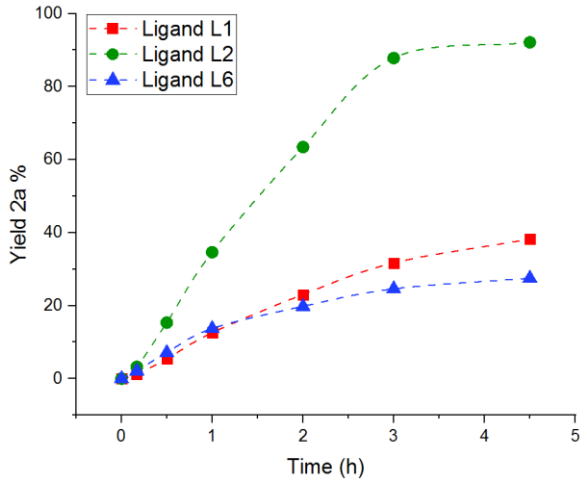
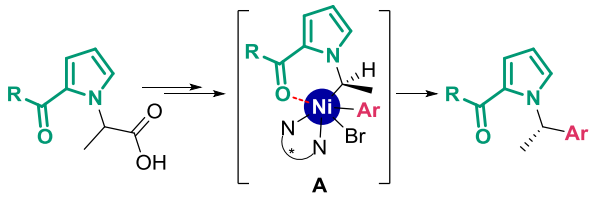


Figure 2. Progression of reaction when using different ligands. Conditions as in Table 1, entries 5 (L1), 6 (L2) and 2 (L6). Yield of 2a determined by SFC analysis of reaction mixtures using an external standard.

With optimised conditions in hand, we next sought to define the scope of the methodology (Scheme 2). Inspired by the good stereocontrol obtained by the Fu and MacMillan groups on carbamate-protected aminoacids (Scheme 1b), we hypothesised that the carbamate could play a role as a coordinating moiety in such systems.[10d] We thus envisaged that the introduction of a directing group in C2 position on the heterocycle might have similar benefits.[20] Such a system could provide an additional binding site for the heterocyclic-alkyl fragment to the nickel centre, increasing rigidity in some key intermediate complexes of the catalytic cycle (Scheme 3, hypothetical intermediate **A**).

Scheme 3. Hypothetical chelation of the alkyl radical to Ni thanks to a directing group on the heterocyclic moiety.



Indeed, an increased stereocontrol is observed when a carbonyl functionality is introduced on the heterocycle: ketone **2b** and amide **2d** are obtained in 92:8 and 91:9 e.r. respectively. However, reduced reactivity is observed, and extended reaction times are required to observe useful yields. An ester group does not seem to provide directing group assistance, for **2c** is obtained with 72:28 e.r., similarly to the model compound. A pyridine ring can also behave as a directing group: derivative **2e** is obtained in improved 85:15 e.r. and 22% yield. Unfortunately, imidazole-bearing etomidate analogue **2f** could not be obtained with our method. If the reaction is run with an achiral ligand a 13% NMR yield is obtained. This suggests that a designed catalytic system might be needed for efficient reactivity of imidazole-containing substrates.[21] Pleasingly, pyrazole-containing derivative **2g** was obtained in 57% yield and 68:32 e.r.; as expected, positioning the acetyl group away from the reaction centre does not provide directing group assistance. Replacing the pyrrole with a bulkier indole ring, as for compound **2h**, has a detrimental effect on enantioselectivity when the ligand employed is **L2**. While the reaction goes to completion, the product obtained is almost racemic; however, if **L1** is used some stereocontrol is restored (71:29 e.r.) whilst maintaining good reactivity (77% yield). As further evidence of the concept of using a directing group, azaindole derivative **2i** was obtained in comparable 65% yield and 83:17 e.r. even when using **L2**. The coordinating ability of the additional nitrogen centre must thus overcome the steric hindrance provided by the two fused rings. A xanthine system, such as in **2j**, is also tolerated (77:23 e.r.), even if the product is obtained with 27% yield. A limitation is found when turning to carbazole derivative **2k**. Employing either **L2** or **L1** as ligands, an almost racemic compound is obtained with a good yield. Phthalimide-containing derivative **2l** and the simple diaryl compound **2m** were obtained in trace amount using our standard conditions.

Variations in the alkyl chain were then explored: groups other than methyl such as *n*-butyl, benzyl and 3-methoxy-3-oxopropyl are tolerated on the substrate, affording products **2n**, **2o** and **2q** in 81-87% yield and enantioselectivities close to the model susbtrate's (76:24 e.r. on average). Unfortunately, valine-derived compound **2p** was obtained with very low stereocontrol in 63% yield, suggesting β-substitution on the alkyl chain is not well tolerated. Azaindole derivative **2r**, bearing a *n*-butyl alkyl chain, could also be obtained with results comparable to those for **2i** (62% yield, 82:18 e.r.).

Lastly, an evaluation of aryl bromides was also performed. A range of *para*-substituted electron-poor derivatives can be successfully coupled with the model pyrrole carboxylic acid **1a**. Ketone **2s**, aldehyde **2t**, benzothiazole **2u** and oxadiazole **2v** can all be obtained in very good yields (75-88%) and enantioselectivity comparable to the model susbtrate's (78:22 e.r. on average). Interestingly, the azole groups in **2u** and **2v** are well tolerated, allowing the preparation of these drug-like compounds in an efficient manner. Other substitution patterns, including *ortho*- (**2w**), *meta*,*meta*- (**2x**) and 2-pyridine substitution (**2y**), seem more problematic, affording products in reduced yields and/or enantioselectivity. The use of electron-neutral or electron-rich aryl bromides is not advised, as poor yields are obtained in the former case (compound **2z**, 10% yield), while only traces of the desired reactivity are found in the latter (compound **2aa**). Compound **2ab**, bearing an acetyl directing group, was obtained with 94:6 e.r. but in 34% yield, similarly to **2b**.

In summary, we have demonstrated how α-heterocyclic carboxylic acids can be successfully employed as substrates for the preparation of enantioenriched chiral *N*-benzylated heterocycles, an important class of compounds now accessible using Ni–photoredox dual catalysis. A variety of substrates was examined to find useful trends and limitations. Notably, the combination of yields and enantioselectivity obtained with cheap and easily obtainable chiral PyOx ligands provides large advances over a comparable racemic synthesis (see ESI, Table S12).[22] Subsequent studies will address current issues, particularly regarding

the reduced reactivity of some heterocyclic substrates (e.g. imidazoles) and aryl halides. We anticipate that the modular and stereoconvergent nature of this strategy will allow rapid screening and diversification of structures, especially useful in a drug discovery setting, exploiting the commercial accessibility of aryl bromides and carboxylic acid precursors.

ASSOCIATED CONTENT

Supporting Information

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

General procedures, characterization of products, physical studies, copies of NMR spectra and SFC traces (PDF)

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REFERENCES

(1) Among the 50 best selling drugs containing a 5-membered heterocycle, 8 of them were found to contain an *N*-benzylic heterocyclic moiety, as from Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442.

(2) US Patent 3354173 'Imidazole carboxylates'.

(3) Belelli, D.; Muntoni, A.-L.; Merrywest, S. D.; Gentet, L. J.; Casula, A.; Callachan, H.; Madau, P.; Gemmell, D. K.; Hamilton, N. M.; Lambert, J. J.; Sillar, K. T.; Peters, J. A. *Neuropharmacology* **2003**, *45*, 57.

(4) Xiong, Y.; Guo, J.; Candelore, M. R.; Liang, R.; Miller, C.; Dallas-Yang, Q.; Jiang, G.; McCann, P. E.; Qureshi, S. A.; Tong, X.; Xu, S. S.; Shang, J.; Vincent, S. H.; Tota, L. M.; Wright, M. J.; Yang, X.; Zhang, B. B.; Tata, J. R.; Parmee, E. R. *J. Med. Chem.* **2012**, *55*, 6137.

(5) Selected examples: (a) Jefford, C. W.; de Villedon de Naide, F.; Sienkiewicz, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1069; (b) Janssen, C. G. M.; Thijssen, J. B. A.; Verluyten, W. L. M. *J. Labelled Compd. Rad.* **1987**, *24*, 909; (c) Baumann, M.; Baxendale, I. R. *Eur. J. Org. Chem.* **2017**, 6518; (d) Indian Patent IN 2011CH04309 "A process for the preparation of etomidate".

(6) (a) Laha, J. K.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 8477; (b) Laha, J. K.; Bhimpuria, R. A.; Hunjan, M. K. *Chem. Eur. J.* **2017**, *23*, 2044, (c) Nilsson, I.; Isaksson, R. *Acta Chem. Scand.* **1985**, *B39*, 531.

(7) Orthogonal functionalisation of multiple heteroatoms has been highlighted as one of the challenges for organic synthesis in drug discovery: Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson; D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383.

(8) (a) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617; (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322; (c) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97; (d) Koike, T.; Akita, M. *Inorg. Chem. Front.* **2014**, *1*, 562; (e) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898; (f) Romero, N. A.; Nicewicz, D. A. *Chem Rev.* **2016**, *116*, 10075; (g) Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Acc. Chem. Res.* **2016**, *49*, 1924.

(9) (a) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035; (b) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, Article number: 0052; (c) Cavalcanti, L. N.; Molander, G. A. *Top. Curr. Chem.* **2016**, 374:39, https://doi.org/10.1007/s41061-016-0037-z.

(10) Selected examples: (a) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437; (b) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624; (c) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322; (d) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832; (e) Fan, L.; Jia, J.; Hou, H.; Lefebvre, Q.; Rueping, M. *Chem. Eur. J.* **2016**, *22*, 16437.

(11) Selected examples: (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433; (b) Alam, R.; Molander, G. A. *J. Org. Chem.* **2017**, *82*, 13728; (c) Primer, D. N.; Molander, G. A. *J. Am. Chem. Soc.* **2017**, *139*, 9847; (d) Amani, J.; Sodagar, E.; Molander, G. A. *Org. Lett.* **2016**, *18*, 732.

(12) Selected examples: (a) Nakajima, K.; Nojima, S.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 14106; (b) Gutiérrez-Bonet, A.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. *ACS Catal.* **2016**, *6*, 8004; (c) Buzzetti, L.; Prieto, A.; Roy, S. R.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2017**, *56*, 15039.

(13) Selected examples: (a) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304; (b) Shields, B.; Doyle, A. G. *J. Am. Chem. Soc.* **2016**, *138*, 12719; (c) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, *547*, 79; (d) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. *Nature* **2018**, *560*, 70; (e) Shen, Y.; Gu, Y.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200; (f) Heitz, D. R.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 12715.

(14) For a review on asymmetric radical cross-couplings, see: Wang, K.; Kong, W. *Chin. J. Chem.* **2018**, *36*, 247.

(15) Cheng, X.; Lu, H.; Lu, Z. *Nat. Commun.* **2019**, *10*, Article number: 3549.

(16) Ahneman, D. T.; Doyle, A. G. *Chem. Sci.* **2016**, *7*, 7002.

(17) To the best of our knowledge, the only example of photoredox cross-coupling of such derivatives has been reported in reference 10e. Analogous non-photoredox disconnections were also described in: (a) Molander, G. A.; Ryu, D.; Hosseini-Sarvari, M.; Devulapally, R.; Seapy, D. *J. Org. Chem.* **2013**, *78*, 6648; (b) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem.* **2013**, *125*, 4549; (c) Katritzky, A. R.; Lang, H.; Lan, X. *Tetrahedron* **1993**, *49*, 2829.

(18) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873.

(19) A review on the use of PyOx ligands in asymmetric catalysis: Yang, G.; Zhang, W. *Chem. Soc. Rev.* **2018**, *47*, 1783.

(20) The effect of directing groups in enantioselective Ni-catalysed cross-couplings is well known; see for example (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299 and references cited therein. General reviews on directing groups: (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307; (c) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.

(21) We found that the imidazole ring might interfere with reactivity. Reaction of 1a with 4-bromobenzonitrile in the presence of 1 equivalent of 1-methylimidazole affords 2a in a reduced 60% yield.

(22) Comparing our enantioselective method to the standard racemic procedure (using $Ir(dF(CF_3)_2ppy)_2(dtbbpy)PF_6$ as photocatalyst and dtbbpy as ligand for Ni), the former is shown to afford higher yields of single major enantiomer for a selected range of substrates.