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Atroposelective Chan–Evans–Lam Amination

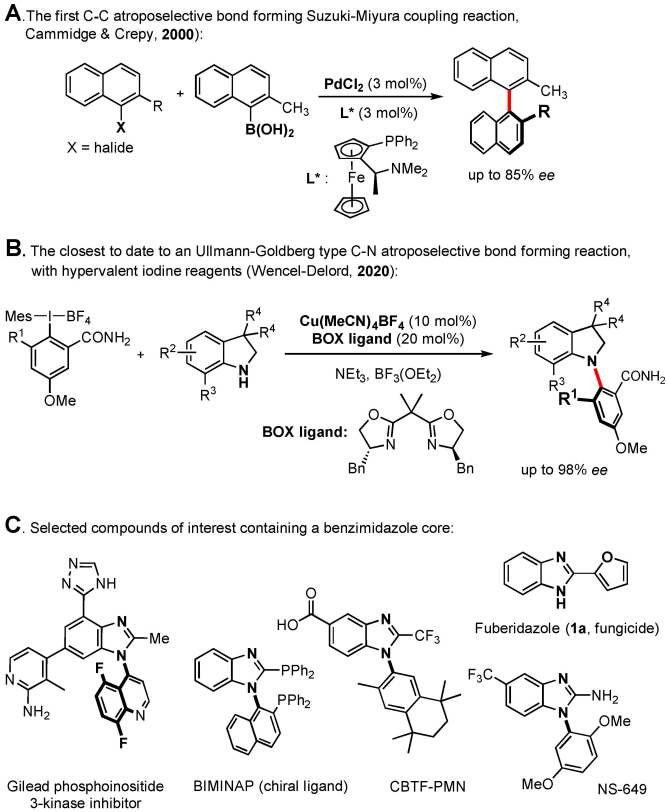
Vinzenz Thönnißen,[a] Johannes Westphäling,[a] Iuliana L. Atodiresei,[a] and Frederic W. Patureau*[a]

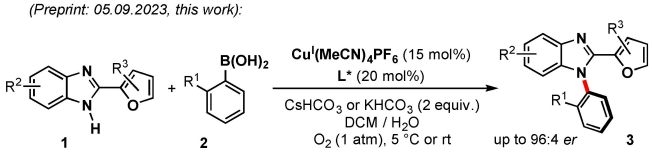
Dedicated to Prof. D. A. Evans (1941–2022)

The synthetic control of atropoisomerism along C–N bonds is a major challenge, and methods that allow C–N atroposelective bond formation are rare. This is a problem because each atropoisomer can feature starkly differentiated biological properties. Yet, among the three most practical and applicable classical amination methods available: 1) the Cu-catalyzed Ullmann–Goldberg reaction, 2) the Pd-catalyzed Buchwald–Hartwig reaction, and 3) the Cu-catalyzed Chan–Evans–Lam reaction, none has truly been rendered atroposelective at the newly formed C–N bond. The first ever Chan–Evans–Lam atroposelective amination is herein described with a simple copper catalyst and newly designed PyrOx chiral ligand. This method should find important applications in asymmetric synthesis, in particular for medicinal chemistry.

Introduction

Atropoisomerism occurs within molecular structures when a hindered rotational barrier causes chirality, often through steric repulsion. This property is important because atropoisomers may express large bioactive differences.[1–6] While C–C bond forming atroposelective coupling reactions have been developed for a long time – the first atroposelective Suzuki-Miyura coupling reaction was reported in the year 2000 (Scheme 1A),[7,8] – C–N atroposelective bond forming reactions remain rare.[9–13] One reason is the pronounced higher electronegativity of nitrogen compared to carbon, therefore often requiring harsher reaction conditions for the final C–N reductive elimination step in the context of metal catalyzed amination reactions. Constructing C–N bonds is nevertheless of paramount importance due to the prevalence of nitrogen and nitrogen based heterocycles in natural as well as synthetic bioactive compounds.[14] In this field, three main methods stand out for their practicality: 1) the Cu-catalyzed Ullmann–Goldberg reaction,[15] 2) the Pd-catalyzed Buchwald–Hartwig reaction,[16–18] and 3) the Cu-catalyzed Chan–Evans–Lam (CEL) reaction.[19–28] These are particularly useful methods because they allow to substitute a C–X (X = halide or pseudo-halide) or carbon–boron functional group (CEL reaction), which are ubiquitous in organic chemistry, into a valuable C–N bond. In other words, the C–X/B functional group in the substrate controls the positional selectivity of the amination





Scheme 1. The quest for the first atroposelective Chan–Evans–Lam C–N bond forming reaction.

[a] V. Thönnißen, J. Westphäling, Dr. I. L. Atodiresei, Prof. Dr. F. W. Patureau
Institute of Organic Chemistry
RWTH Aachen University
Landoltweg 1, 52074, Aachen, Germany
E-mail: Frederic.patureau@rwth-aachen.de
Homepage: https://www.patureau-oc-rwth-aachen.de/

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reaction through specific metalation, which has no other equivalent in the amination toolbox.

In this context, Wencel-Delord and co-authors reported a pioneering Cu-catalyzed C–N atroposelective bond forming reaction in 2020, which is reminiscent of the Ullmann–Goldberg C–N bond forming reaction (Scheme 1B).[29] This method is however limited to the use of highly activated hypervalent iodanes, which starkly contrasts with Ullmann and Goldberg's simple organo-halide substrates. More recently, Wang and co-authors reported the use of highly reactive diazonaphthoquinone substrates under Rh-catalysis.[30] To this day however, none of the three main intermolecular amination methods listed above have ever been rendered atroposelective at the constructed C–N bond, with the notable exception of the Wencel-Delord method,[29] which therefore still constitutes a major and long elusive objective.

Results and Discussion

The Chan–Evans–Lam (CEL) reaction features key advantages compared to other amination methods, such as milder reaction conditions, often at room temperature. Moreover, copper is considerably less scarce than palladium,[31] and the highly versatile chemistry of C–B bonds has been extensively developed in the past few years.[32–41] Organoboron substrates therefore constitute a large and reliable platform in synthetic method development. These arguments make the CEL reaction a particularly attractive target for C–N atroposelective bond formation. In this context, we decided to focus primarily on benzimidazole N-nucleophiles due to their prevalence in a large number of important bioactive targets, in particular the fungicide Fuberidazole (substrate **1a**, Scheme 1C & 1D).[42–48]

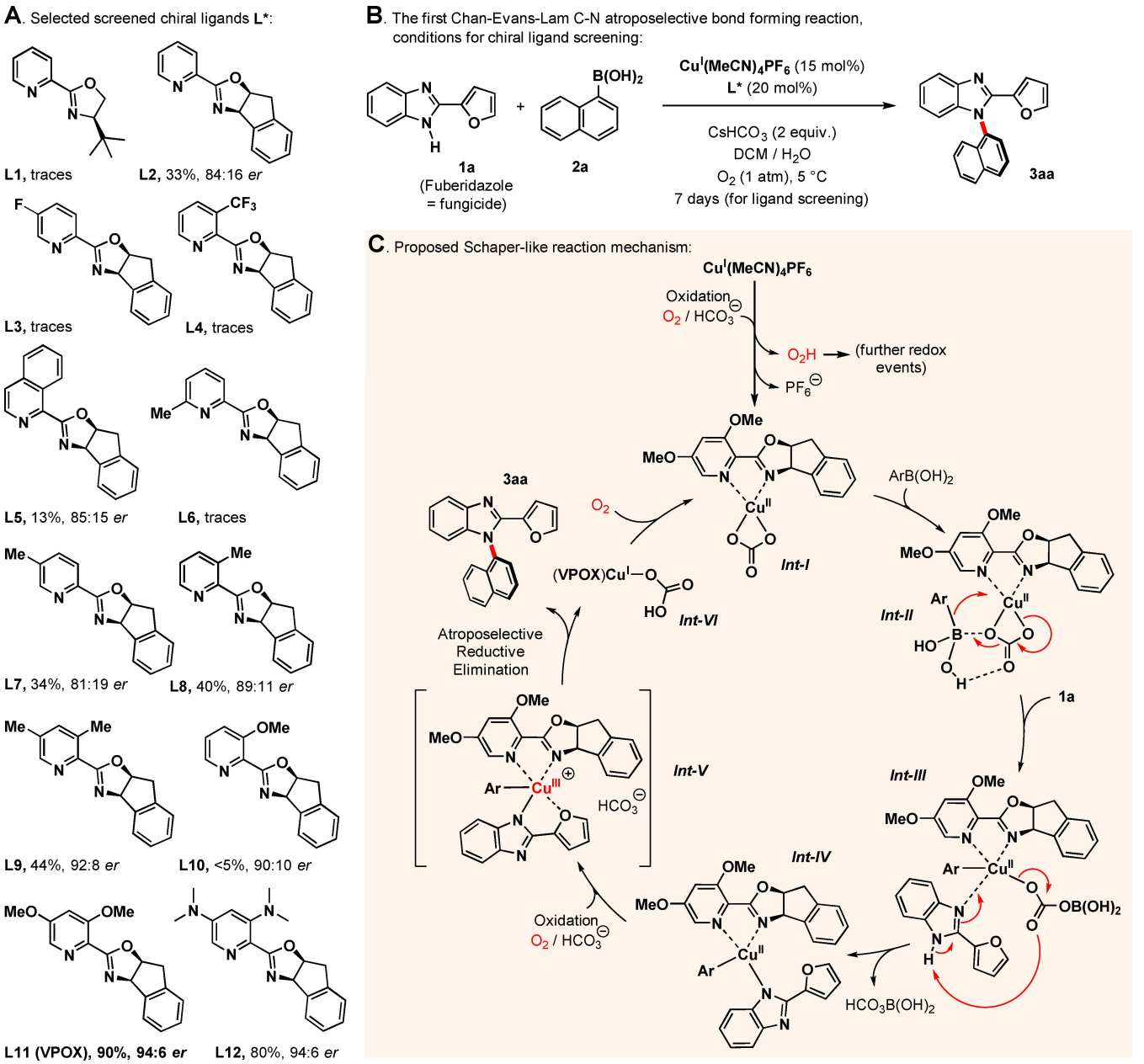
After screening various conditions such as solvent, base, Cu-catalyst precursor, ligand type, and temperature (see SI, Table S1), we then focused on the design of the chiral ligand. The best results in terms of both yield and enantiomeric ratio (*er*) of the product were obtained with chiral pyridine-oxazoline (PyrOx) bidentate ligands, which are easily prepared (see SI) and have previously been successful in some elegant enantioselective applications.[49–50] Among the herein screened chiral ligand structures (**L1** to **L12**, Scheme 2A and 2B), electron donor substituents on the 3,5 positions of the pyridine moiety were found to be critical for both conversion and enantiomeric excess (**L9**, **L11**, **L12**, for more chiral ligand screening, see the SI on p. S16). In particular, the 3,5-dimethoxy-substituted scaffold **L11** proved optimal. We refer to it as **VPOX** for convenience. While the 3,5 substitution pattern should not strongly affect the basicity of the pyridine moiety, it should impact the basicity of the oxazoline moiety through electron-donor effects. The thus increased basicity of the catalyst may in turn facilitate several key elementary steps in the reaction, such as C–B and N–H bond activation, or Cu(II) to Cu(III) intermediate oxidation en route to the C–N reductive elimination step.

Based on these observations, as well as on the insightful mechanistic investigations by Schaper and team regarding the Cu-catalyzed CEL reaction,[51] we propose a preliminary Cu(I)/Cu(II)/Cu(III) catalytic cycle as depicted in Scheme 2C. The Cu(I) precatalyst would first undergo oxidative ligand exchange with the carbonate base towards Cu(II) intermediate **Int-I**. The fact that neither the oxidation state of the precatalyst nor the nature of its initial counterion seem to strongly affect the catalytic performance (see SI, Table S1), reinforces this scenario. The carbonate base was however found to be essential. The C–B bond activation step would then be triggered by supramolecular interactions with the basic carbonate ligand (intermediate **Int-II**), analogously to the Schaper mechanism, towards C–Cu(II) intermediate **Int-III**. The second basic site of the remaining carbonate ligand would then deprotonate the incoming benzimidazole N–H substrate towards C–Cu(II)–N species **Int-IV**. This step is feasible due to prior acidification of the N–H bond through coordination to the Cu center, and may run through a CMD-like (concerted metalation deprotonation) mechanism.[52] Further one electron oxidation of **Int-IV** towards highly activated Cu(III) intermediate **Int-V** would deliver the necessary driving force to release the C–N atroposelective reductive elimination product as well as Cu(I) intermediate **Int-VI**. The latter would then be re-oxidized toward active species **Int-I**. The rigid and bidentate nature of both the chiral ligand, **VPOX**, and the benzimidazole substrate would be decisive for high asymmetric induction during the reductive elimination step. Moreover, the absence of non-linear effects in this reaction are in agreement with a mononuclear Cu-catalyzed mechanism.[53]

With the reaction conditions in hand we then explored the substrate scopes (**3aa**–**3ra** & **3ab**–**3aj**, Scheme 3). At first, variations of 2-substituted benzimidazoles were prepared and investigated (**3aa**–**3ra**). Thus, it soon became apparent that an oxygen based chelating functional group generally leads to superior results. The highest enantioselectivity was for instance achieved with a 5-methyl furyl moiety (**3ca**, *er* = 96:4).[54] This level of enantioselectivity is exceptional for such a challenging process: the atroposelective Chan–Evans–Lam amination, as none whatsoever has ever been achieved before for this critically important reaction. The absence of the furyl directing group, such as in product **3ma** bearing only a simple 2-methyl substituent, leads to modest yield and enantioselectivity. The role of this directing group may thus be to reduce rotational freedom at the critical enantioselective step. Other directing groups, however, such as 2-thiophene (product **3pa**), or 2-pyridine (**3qa**), proved poisonous for the catalyst. Interestingly, 2-acetylbenzimidazole is also suitable for the reaction, albeit with a somewhat decreased *er* (85:15, **3ga**). In general, electron-donating substituents lead to superior results. Noteworthy are the products **3ja** and **3ka**, which were isolated as mixtures of regioisomers due to the unsymmetrical character of their benzimidazoles moieties, however with good enantioselectivities. Importantly, indole N–H substrates were not found applicable due to their rapid oxidative decay in these reaction conditions (**3ra**). We are currently working on addressing this particular challenge.

Subsequently, the aryl boronic acid scope was investigated (**3ab**–**3aj**). Notably, a phenanthrene moiety (**3ae**) was successfully accommodated, as well as a series of important *ortho* substituted phenyl boronic acids.

All our attempts to determine absolute configurations by means of x-ray crystallography failed so far. However, the absolute configuration of the major enantiomeric product obtained from (1*R*,2*S*)-**VPOX** was successfully determined by means of CD spectroscopy and theoretical calculations for **3ga**. The obtained



Scheme 2. Chiral ligand screening and proposed reaction mechanism. **A.** Selected screened chiral ligands. For more screened chiral ligands see the SI p. S16. **B.** Reaction substrates and conditions for chiral ligand screening. **C.** Proposed reaction mechanism based on the investigations of Schaper and co-authors.[51]

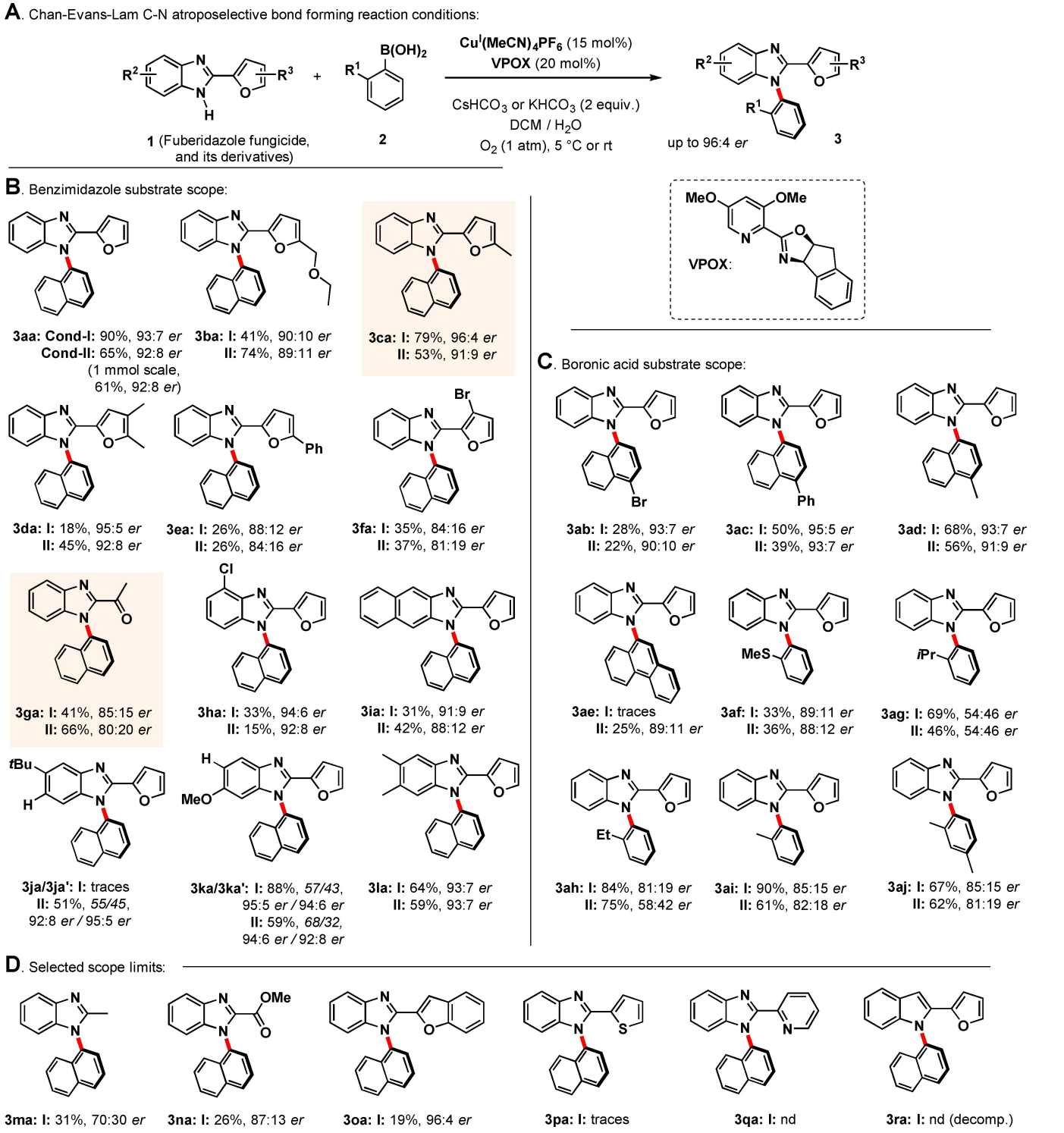
data is in excellent agreement with the (*R*)-**3ga** configuration (Figure 1, see also SI). In addition, rotational barriers of products **3aa** and **3ai** were determined to be above 30 kcal/mol using both computational tools as well as experimental measurements, confirming the atropostability of these products. The corresponding racemization half-lives at 25 °C were estimated at 137 and 24 years, respectively (Figure 2, see also SI).

Conclusions

In conclusion, we developed the first ever Chan–Evans–Lam C–N atroposelective coupling, with unprecedented levels of enantioselectivity for such a challenging reaction concept. We have moreover identified a new chiral ligand, **VPOX**, which should find further applications in asymmetric catalysis.[55–62] Overall, our results[63,64] should serve as a blueprint for further C–N atroposelective bond forming reactions, in particular under Cu-catalysis,[65–70] and related systems.[71–74]

Supporting Information[75–104]

Synthetic methods, NMR, IR, HRMS, chiral analytical HPLC characterization of the products, ^{1}H and ^{13}C NMR spectra. The authors have cited additional references within the Supporting Information.[75–104]



Scheme 3. The first Chan–Evans–Lam C–N atroposelective bond forming reaction, examples, isolated yields. (**A**) General reaction conditions **I**: **1** (0.1 mmol), **2** (0.2 mmol, 2 equiv.), $Cu(MeCN)_4PF_6$ (15 mol%), **VPOX** (20 mol%) and $CsHCO_3$ (2 equiv.) were stirred under oxygen atmosphere in DCM/H_2O (0.75 mL/0.1 mL) at 5 °C for 7 days. General reaction conditions **II**: **1** (0.1 mmol), **2** (0.2 mmol, 2 equiv.), $Cu(MeCN)_4PF_6$ (15 mol%), **VPOX** (20 mol%) and $KHCO_3$ (2 equiv.) were stirred under oxygen atmosphere in DCM/H_2O (0.9 mL/0.1 mL) at rt for 3 days. (**B**) Variation of the N–H substrate. (**C**) Variation of the C–B substrate. (**D**) Selected scope limits.

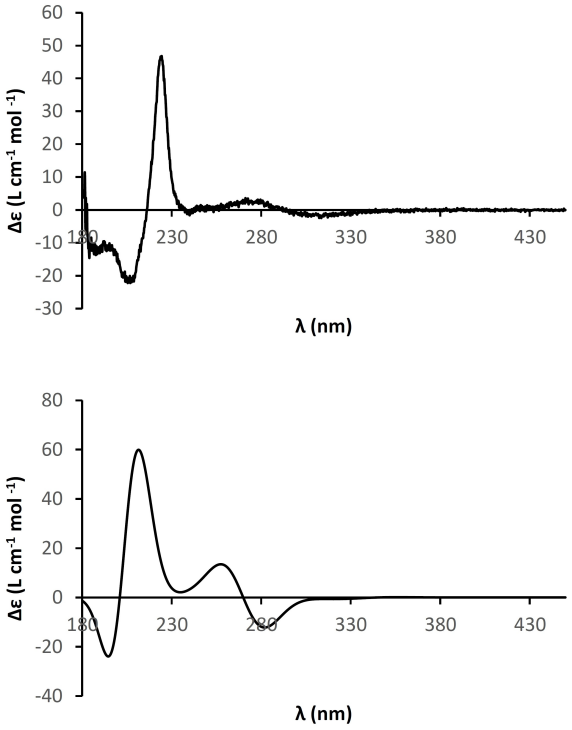


Figure 1. Experimental CD-spectrum of **3 ga** (85 : 15 *er*, top), and averaged calculated CD-spectrum of (*R*)-**3 ga** at TD-DFT/cam-B3LYP/6-31 + G**//B3LYP/6-31G* level; CD spectrum averaged over 14 conformations with different dihedral angles θ1 using the cam-B3LYP/6-31 + G**//B3LYP/6-31G* relative energies (beneath, see SI, Figures S4, S5, and S6).

3aa
$\Delta G^{\ddagger}_{(calculated)}$ = 33 kcal.mol^{-1}
$\Delta G^{\ddagger}_{(measured)}$ = 31 kcal.mol^{-1}
$t_{1/2}$ = 137 years at +25 °C

3ai
$\Delta G^{\ddagger}_{(calculated)}$ = 33 kcal.mol^{-1}
$\Delta G^{\ddagger}_{(measured)}$ = 30 kcal.mol^{-1}
$t_{1/2}$ = 24 years at +25 °C

Figure 2. Racemization barrier of **3 aa** and **3 ai** (see SI).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Chan–Evans–Lam reaction · atroposelective amination · enantioselective catalysis · PyrOx ligand · VPOX

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