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Organocatalysis

Bifunctional Iminophosphorane Catalyzed Amide Enolization for Enantioselective Cyclohexadienone Desymmetrization

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Abstract: The organocatalytic enolization of 2-arylacetamides, followed by an enantioselective intramolecular conjugate addition to tethered 2,5-cyclohexadienones, yielding 3D fused *N*-heterocycles, is described. The transformation represents the first strong activating group-free activation of carboxamides via α-C–H deprotonation in a metal-free, catalytic, and enantioselective reaction, and is achieved by employing a bifunctional iminophosphorane (BIMP) superbase.

Carboxamides are commonly occurring motifs in numerous natural products, biomolecules, and pharmaceuticals. Due to resonance stabilization between the carbonyl group and the lone pair of electrons on the nitrogen atom, enolate formation is typically more challenging as compared to aldehydes and ketones; the α-protons of amides (pK_a in dimethyl sulfoxide (DMSO) ≈26.6 for *N,N*-dimethyl-2-phenylacetamide)[1] are significantly less acidic than those of their corresponding aldehydes or ketones (pK_a in DMSO ≈19.8 for 2-phenylacetone).[2] Accordingly, the α-deprotonation of amides for downstream reactivity with electrophiles would typically involve the use of stoichiometric amounts of strong non-nucleophilic bases such as lithium diisopropylamide (LDA) or potassium bis(trimethylsilyl)amide (KHMDS) to generate their requisite metal enolates.[3] A catalytic amide enolization method for the enantioselective installation of an electrophile at the α-position can be a valuable atom-economical tool in chemical synthesis. To this end, a few transition metal catalyzed methods have been developed using both activated and unactivated "simple" carboxamide substrates.[4–6] A recent study by Fu describes the α-alkylation of simple amides with alkyl iodide electrophiles, using a chiral nickel catalyst in a two-step procedure involving the stoichiometric preformation of a racemic Reformatsky reagent intermediate.[7] There are also a few reactions requiring the simultaneous use of an anionic base and a chiral organocatalyst/ligand. In 2015, Kobayashi reported the first catalytic enantioselective conjugate addition of simple amides to α,β-unsaturated amides, utilising a catalyst system composed of KHMDS and a macrocyclic chiral crown ether.[8] More recently, Terada reported an enantioselective conjugate addition of activated α-thioacetamide substrates to various unsaturated electrophiles using a catalyst system consisting of sodium *tert*-butoxide (NaO^{t}Bu) and a chiral ureate (Scheme 1b).[9] Necessarily, both of these methods would involve the formation of a metal amide enolate as the key nucleophilic species. Notwithstanding these important contributions, we aimed to develop the first metal-free amide enolization for the enantioselective coupling with a suitable electrophile. Without strong activating groups, the deployed catalyst would have to be sufficiently Brønsted basic to deprotonate the high pK_a amide pronucleophile to form the reactive amide enolate. We envisioned that our bifunctional iminophosphorane (BIMP) superbase catalysts could be suitable candidates for promoting amide enolization and hence enabling a downstream enantioselective reaction with a suitable electrophile, by virtue of their strong basicity (pK_a≈25 in CH_3CN). These chiral organocatalysts were disclosed by our group in 2013 and contain a highly basic and tunable iminophosphorane moiety prepared in situ in a Staudinger reaction between an azide and a trivalent phosphine. In turn, the iminophosphorane moiety is connected to a hydrogen bond donor (HBD) group by a chiral backbone and together the three modules allow ready coarse and fine tunability.[11,12] Pendant 2,5-cyclohexadienones were identified as potentially suitable electrophiles for exemplifying this catalytic amide enolization reaction. A number of methods for their enantioselective desymmetrization have been discovered, which have mostly involved reactions with heteroatom-centred pronucleophiles or other pronucleophiles with relatively low pK_a values, using cinchona alkaloid derivatives as organocatalysts (Scheme 1c).[13,14] By tethering an amide pronucleophile to the 4-position of the cyclohexadienone, the amide enolate, formed during deprotonation by the BIMP catalyst, can undergo an intramolecular conjugate addition reaction. A bicyclic dearomatized oxindole product containing 3 contiguous stereogenic centres would be formed in this reaction. Sp^3-rich fused *N*-heterocycles are common structural elements found in a wealth of bioactive natural products (Scheme 1d), and therefore, the current methodology could be of immediate value in medicinal chemistry programs and total synthesis.[15] BIMP catalysts have been proven over the years to be effective in various challenging enantioselective

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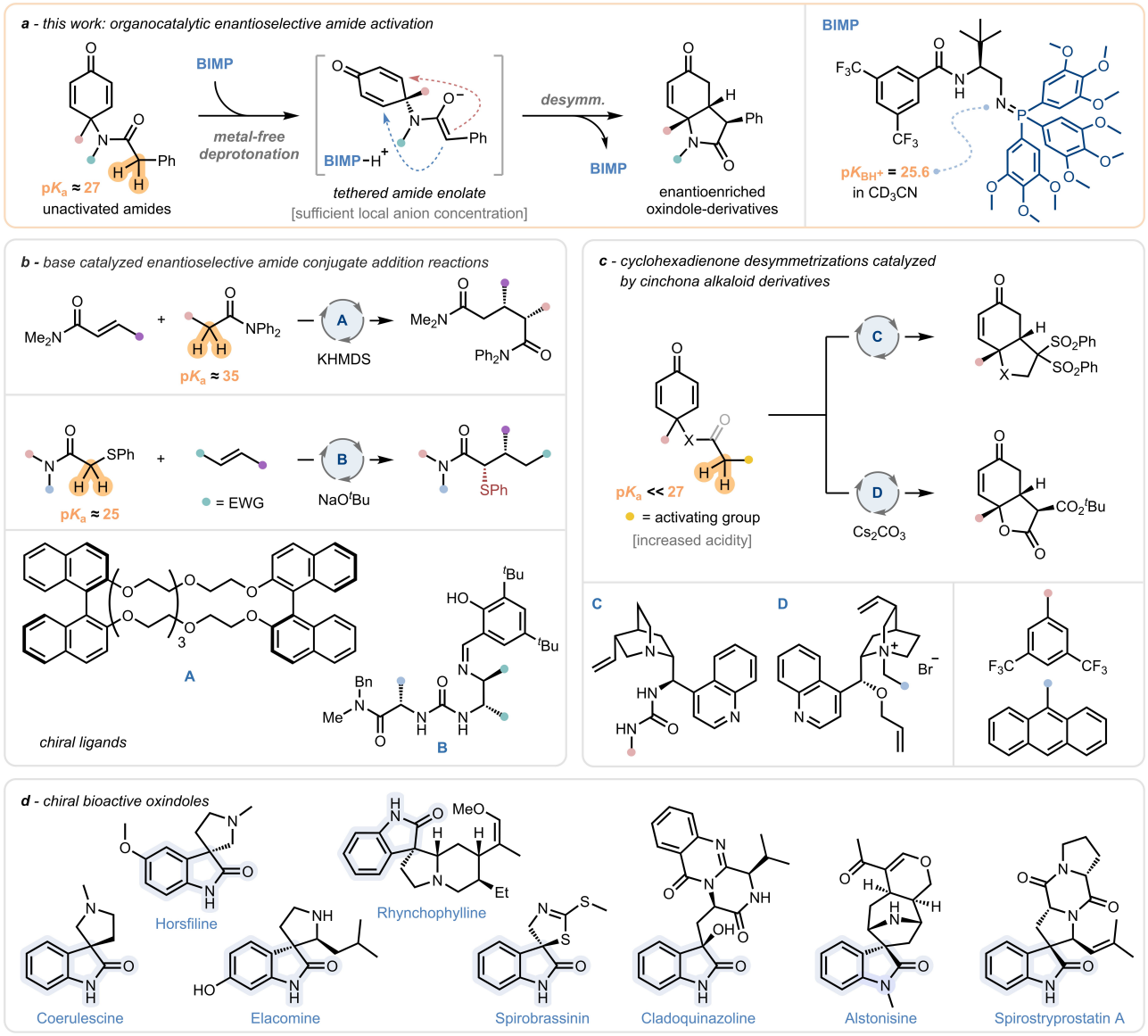

Scheme 1. BIMP catalyzed cyclohexadienone desymmetrization via metal-free amide deprotonation (this work, **a**). Base catalyzed enantioselective amide conjugate addition reactions (**b**). Selected organocatalytic cyclohexadienone desymmetrization reactions (**c**). Chiral bioactive oxindoles . pK_a values are reported in DMSO, unless otherwise noted.

intramolecular and intermolecular conjugate addition reactions to unsaturated carbonyl compounds,[16,17] and we were keen to explore their potential with high pK_a pronucleophiles. We reasoned that the deprotonation of the high pK_a amide by the BIMP catalyst was likely to be the rate limiting step in our proposed reaction. As the 5-exo-trig intramolecular conjugate addition of the amide enolate to the cyclohexadienone was likely to be relatively fast, the cyclohexadienone would effectively function as an intramolecular "trap" for the amide enolate, thereby facilitating the formation of the desired dearomatized oxindole products by exploiting a high local anion concentration (Scheme 1a). For the initial exploration into the enantioselective intramolecular addition of amides to 2,5-cyclohexadienones, we selected cyclohexadienone-tethered *N*-benzyl-2-phenylacetamide (**1a**) as the model substrate (Table 1). A BIMP catalyst screen was carried out with reactions run at 0.1 mmol scale in 0.5 M diethyl ether (Et_2O) with 10 mol % catalyst loading at room temperature for 24 or 48 hours. L-*Tert*-leucine derived catalysts bearing a single stereogenic centre and an amide HBD were revealed to be superior in terms of both reactivity and stereoselectivity compared to others in our library. Catalyst **B1** furnished the desired oxindole derivative **2a** in >99 % conversion, 78.5:21.5 enantiomeric ratio (e.r.) and 12:1 diastereomeric ratio (d.r.) (Table 1, entry 1). The trivalent phosphine used in the Staudinger reaction to form the BIMP catalyst was then varied. The replacement of the *para*-methoxyphenyl (PMP) substituents around the phosphorus atom with 3,4,5-trimethoxyphenyl substituents lead to an increase in selectivity (**B2**, 85:15 e.r. and >20:1

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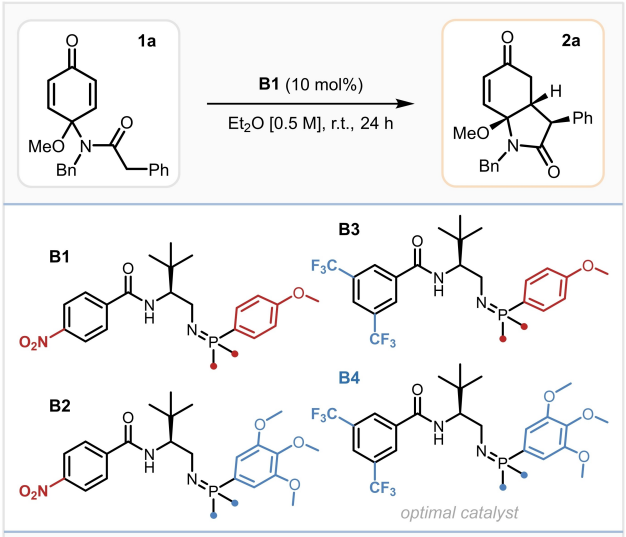
Table 1: Catalyst development and optimization of reaction conditions. All reactions were run on a 0.1 mmol scale.



entry	changes in conditions	conversion (%)[a]	e.r.	d.r.
1	n / a	>99	78.5:21.5	12:1
2	**B2** catalyst	96	85:15	>20:1
3	**B3** catalyst	>99	89:11	12:1
4	**B4** catalyst	>99	95:5	>20:1
5	toluene solvent, **B4** catalyst	>99	96:4	>20:1
6	TBME solvent, **B4** catalyst	>99	96.5:3.5	>20:1

[a] Conversion determined by ^{1}H NMR analysis by comparing starting material and product peaks. d.r. determined by ^{1}H NMR analysis by comparing major and minor diastereomer peaks. e.r. determined by HPLC on a chiral stationary phase. Omitted iminophosphorane substituents are identical to the substituents shown.

d.r., entry 2). Replacing the HBD substituent in catalyst **B1** to a 3,5-bis(trifluoromethyl)-phenyl group yielded catalyst **B3**, which furnished **2a** in an increased enantioselectivity (89:11 e.r.), but a slightly lowered diastereoselectivity (12:1 d.r., entry 3). Finally, combining the best features of catalysts **B2** and **B3** gave rise to BIMP **B4**, which provided product **2a** quantitatively and in excellent stereoselectivity (95:5 e.r. and >20:1 d.r., entry 4). A thorough investigation into the reaction solvent and conditions revealed that the highest selectivity was obtained when *tert*-butyl methyl ether (TBME, 96.5:3.5 e.r. and >20:1 d.r., entry 6) was employed as the reaction solvent, with toluene (96:4 e.r., entry 5) being a good alternative. Notably, the reactions were conducted under benchtop conditions without the need for specialized techniques, highlighting the robustness of BIMP catalysts. After successfully optimizing the model reaction, the scope of the methodology was explored. Reactions were conducted on a 0.1 mmol scale (Scheme 2). First, using substrates **1b–f**, the effects of the substitution pattern on the aromatic ring adjacent to the α-carbon of the amide were investigated. Switching the model substrate to electron-donating 4-OMe substituted compound **1b** had a significant effect on the reactivity, and the reaction had to be heated to 50 °C to achieve full conversion to **2b**. However, the selectivity remained high at 96:4 e.r. and >20:1 d.r., which was remarkable considering the temperature increase as compared to the model reaction. Product **2c** containing an electron-withdrawing 4-F substituent was formed in excellent yield and stereoselectivity with 95:5 e.r. and >20:1 d.r. under the standard conditions. A 4-nitrophenyl moiety in the α-position had a detrimental effect on the reaction, and product **2d** was furnished in 73 % yield, 67.5:32.5 e.r. and 9:1 d.r. under the optimized conditions. Additional time-resolved NMR experiments revealed no change in the e.r. and d.r. of **2d** over time, implying the irreversibility of the conjugate addition step. Furthermore, when the major diastereoisomer of **2d** was isolated and resubjected to the reaction conditions, it rapidly equilibrated back to a 9:1 mixture of diastereoisomers, suggesting rapid and reversible proton exchange between **2d** and **B4**, and therefore that the observed reaction diastereoselectivity is under thermodynamic control.[18] A methoxy substituent in the 3-position in **1e** led to a smooth reaction at room temperature, with the product forming in 97:3 e.r. and 20:1 d.r. A bulkier 2-Br substituent in **1f** similarly had no considerable effect on efficiency and selectivity, with **2f** formed in 99 % yield, 96:4 e.r. and >20:1 d.r. Changing the phenyl ring in **1a** to 2-thiophene in **1g** had a somewhat detrimental effect on selectivity, with **2g** formed in 97 % yield but 78.5:21.5 e.r. and 8:1 d.r. Changing this group to a terminal alkene in **1h** led to both the desired conjugate addition and a subsequent stereoselective 1,3-prototropic shift to form internal alkene **2h** in 69 % yield, 85.5:14.5 e.r. as a single diastereoisomer. Next, the effects of the substituents on the nitrogen atom of the amide were investigated (**1i–o**). Pleasingly, yields and selectivities remained high across a range of substrates, with only **2o** formed in a moderate enantioselectivity of 85.5:14.5 e.r., likely due to the bulkier substituent on the nitrogen atom. Spirocyclic substrate **1p** underwent the transformation at an elevated temperature and increased catalyst loading, and product **2p** was obtained in 55 % yield and 80:20 e.r. Finally, the effect of the substituent attached to the quaternary centre in substrates **1q** to **1s** was investigated. Pleasingly, stereoselectivities remained high across all substrates. Reactivity, however, decreased with increasing bulk; the reaction of **1s** had to be heated to 50 °C with increased catalyst loading at 15 % to achieve full conversion to product **2s**. After demonstrating the scope of our methodology, the model reaction was successfully scaled up to a 3 mmol scale (Scheme 3). For this reaction, the catalyst loading was reduced to 5 mol % (from 10 mol % previously), and the reaction time was increased to 48 h. Full conversion was achieved within that time and product **2a** was obtained in 96 % isolated yield and 96:4 e.r. Recrystallization from MeOH afforded **2a** in 74 % yield and 99.5:0.5 e.r. as a single diastereomer, which was confirmed by single crystal X-ray diffraction analysis.[19] The methoxy group on **2a** smoothly underwent a Lewis acid-catalyzed nucleophilic substitution with TMSCN to form all carbon quaternary stereogenic centre-containing product **3a** in 62 % yield, moderate d.r. but with no erosion in e.r. The stereochemical configuration of the major diastereoisomer was confirmed by single crystal X-ray diffraction analysis.[19] Product **2a** efficiently reacted

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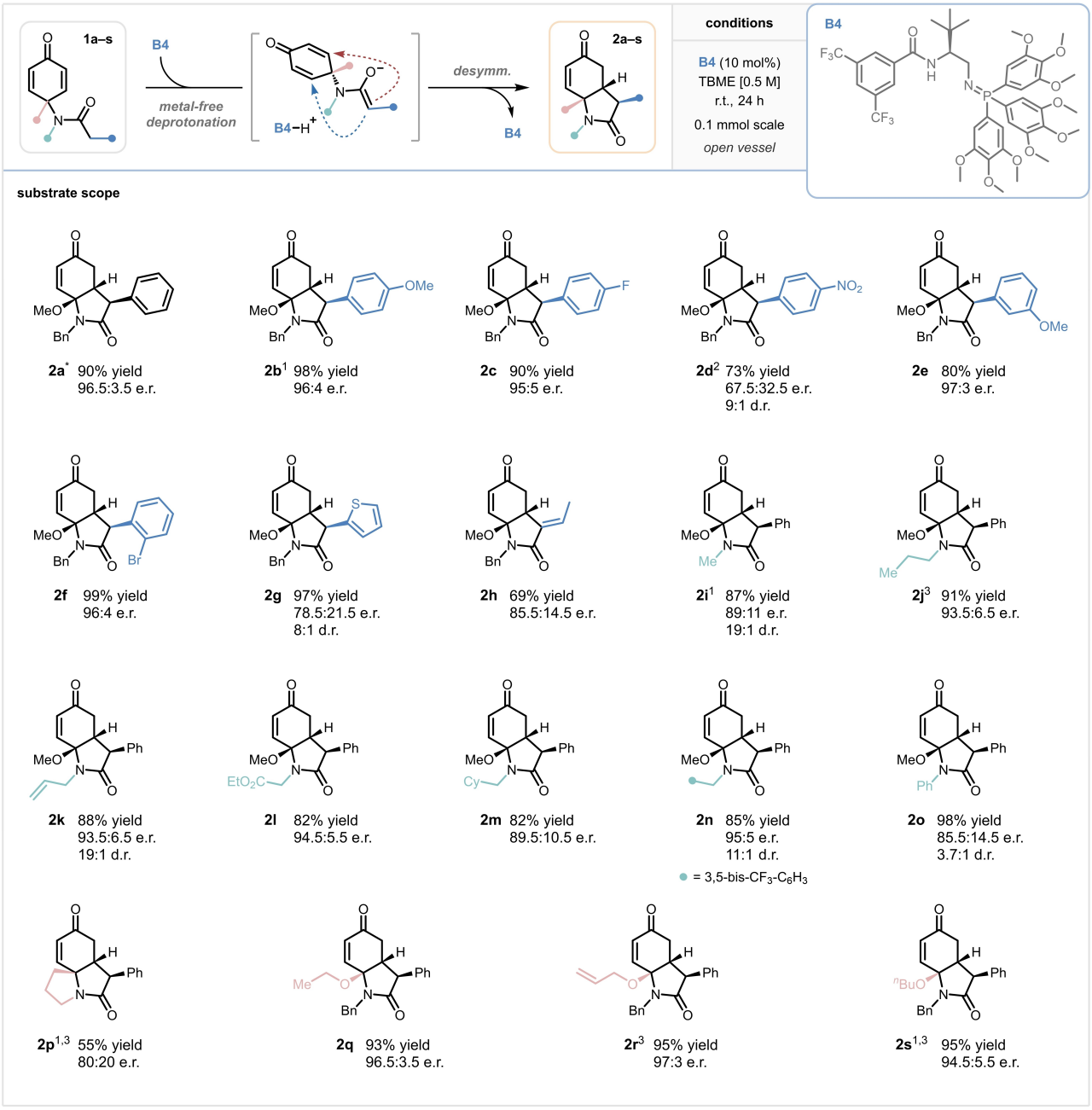

Scheme 2. Substrate scope. *Absolute stereochemical configuration was determined by single crystal X-ray diffraction analysis. Isolated yields. >20:1 d.r. where d.r. is not mentioned. e.r. determined by HPLC on a chiral stationary phase. [1] Reaction carried out at 50 °C. [2] Reaction quenched after 5 min. [3] 15 mol% catalyst loading.

with 4-methylthiophenol in the presence of triethylamine, forming sulfa-Michael adduct **3b** in excellent yield, and near perfect enantiospecificity (e.s.), albeit with low diastereoselectivity. The enone C=C bond in **2a** was selectively hydrogenated using Pd/C to form cyclohexanone **3c** in quantitative yield and 100% e.s. The carbonyl group was chemoselectively reduced using $NaBH_4$ in combination with $CeCl_3$ to form secondary allylic alcohol **3d** in 73% yield, 1.2:1.0 d.r. and 98% e.s. (major diastereoisomer). It is worth noting that both **3b** and **3d** were formed in 1.2:1 d.r., showing essentially no preference for addition to one face over the other. Finally, dienyl triflate **3e**, which was formed under standard conditions in 95% yield and with no loss in enantiopurity, underwent a rapid CuI catalyzed Kumada-type coupling reaction with MeMgBr to yield methylated diene **4a** in 83% yield and 100% e.s. as a single diastereoisomer. In summary, we have developed the first organocatalytic strong activating group-free amide enolization reaction for the enantioselective intramolecular conjugate addition to 2,5-cyclohexadienones. This powerful BIMP catalyzed methodology tolerates a good range of substituents and can be carried out on a gram-scale. The dearomat-

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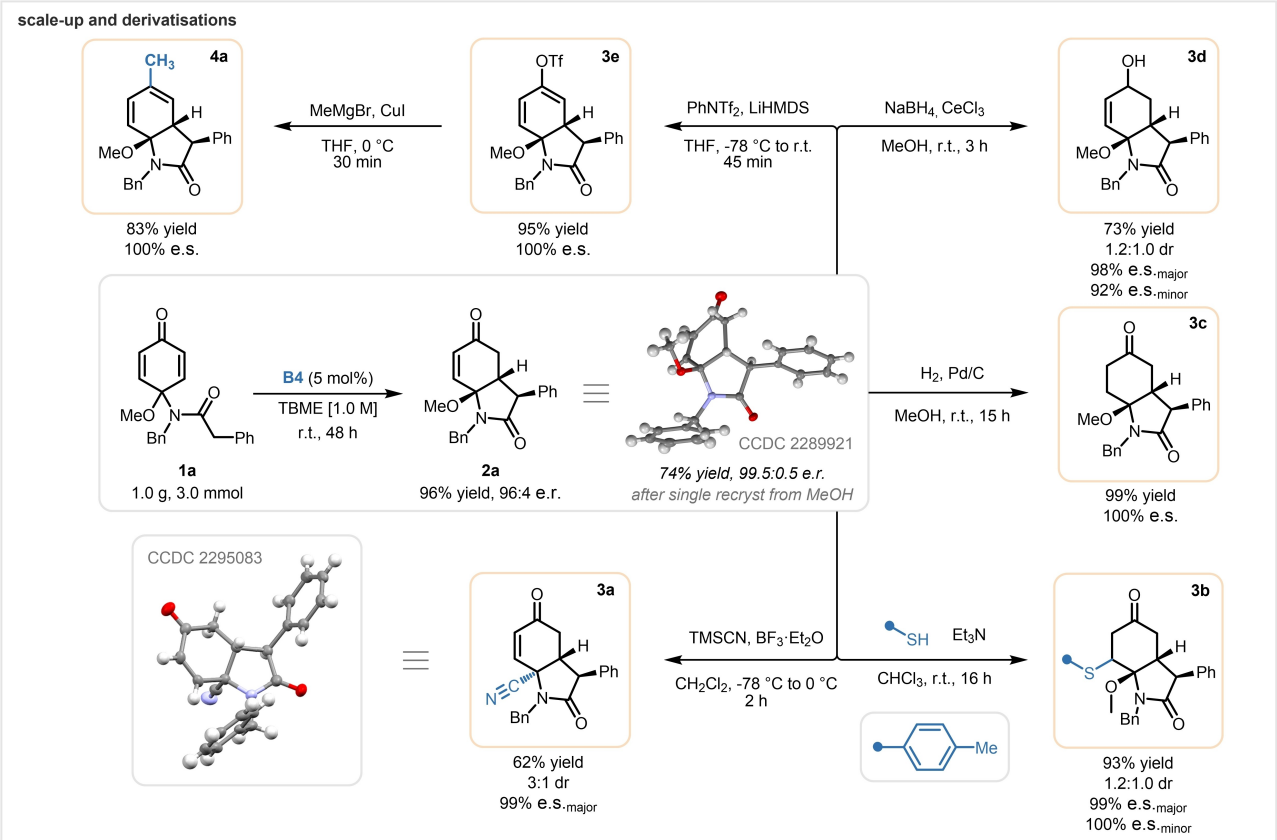

Scheme 3. Preparative scale synthesis and further functionalization of dearomatized oxindole products.

ized oxindole products can be further functionalized in a variety of ways, allowing the rapid synthesis of highly enantioenriched semi-saturated 3D *N*-heterocycles.

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Conflict of Interest

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.

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