Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Regioselective Synthesis of Chirally Enriched Tetrahydrocarbazolones and Tetrahydrocarbazoles

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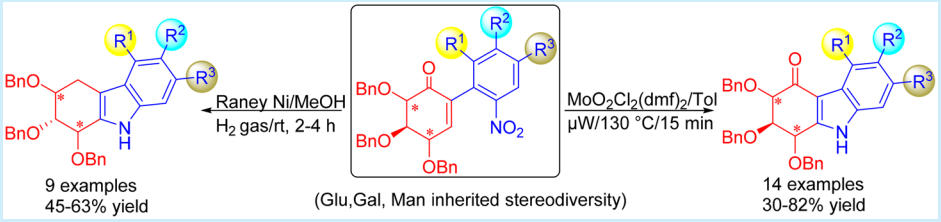
Supporting Information



ABSTRACT: A new one-step, reagent-directed regioselective synthesis of chirally enriched tetrahydrocarbazolones and tetrahydrocarbazoles from a common type of substrate has been developed. The salient features of this method include inherited stereodiversity, a broad substrate scope, a quick reaction time, and a benign catalyst. The method is applicable to the synthesis of a bioactive cryptosanguinolentine precursor.

Carbazoles and their derivatives are important nitrogen-containing heterocyclic compounds having a tricyclic structure that are widespread in nature.[1] Tetrahydrocarbazolone is a subclass of carbazoles that consists of an indole ring fused at the C-2 and C-3 position with a cyclohexanone. Carbazolones are key intermediates in the synthesis of natural product alkaloids such as murryaquinone A[2] as well as pyrayaquinone A and B.[3] Compounds with a carbazolone nucleus exhibit diverse biological activities including serving as HIV-integrase inhibitors,[4a] potassium channel blockers,[4b] and antipsychotics.[4c] Furthermore, chiral tetrahydrocarbazolones are one of the most important structural motifs present in drug molecules. (*R*)-Ondansetron is a 5-HT3 receptor antagonist, used for treatment of nausea and vomiting, caused during chemotherapy in cancer patients (Figure 1). Its *S*-isomer and racemic mixture are not suitable for medical use.[5] Sorazolone A is a chirally functionalized tetrahydrocarbazolone isolated from *Sporangium cellulosum* strain Soce375, which exhibits cytotoxicity against a mouse fibroblast cell line.[6] Similarly, there are chiral tetrahydrocarbazole (CTHC) based bioactive molecules currently used as drug candidates (Figure 1).[7]

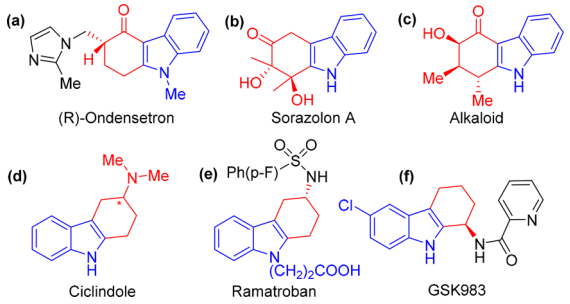


Figure 1. Some drugs and natural products with chirally enriched tetrahydrocarbazolones (a−c) and tetrahydrocarbazoles (d−f).

Considering the biopotential of tetrahydrocarbazolones and tetrahydrocarbazoles, several groups have developed various methods for the synthesis of these derivatives. The basic method is the Fisher indole synthesis;[8a] however, the drawbacks of this method are the highly acidic conditions and poor regioselectivity it displays.[8b] Later transition metal (Pd and Cu)-catalyzed intramolecular cyclizations of *o*-halo aryl enaminones were also reported.[9] Wang and co-workers have also reported metal-free hypervalent (III) iodine promoted oxidative annulation of 2-aryl enaminones for carbazolone synthesis.[10]

Reductive cyclization is another important method for carbazolone synthesis. Söderberg and co-workers have further reported a Pd-catalyzed reductive *N*-heteroannulation for the synthesis of carbazolones, but it requires CO.[11a] Yao and co-workers have developed an Fe/AcOH mediated intramolecular reductive cyclization of 3-hydroxy-2-(2-nitrophenyl) enones for carbazolone synthesis.[11b] Recently, Zhu and co-workers have accomplished an efficient synthesis of substituted carbazolones by reductive cyclization of chirally substituted (2-nitro phenyl) enones in the presence of aqueous $TiCl_3$ and NH_4OAc.[11c] However, there are only a few synthetic reports available for the synthesis of chirally enriched tetrahydrocarbazolones.[12] The development of an efficient method for

Received: May 25, 2018

DOI: 10.1021/acs.orglett.8b01656
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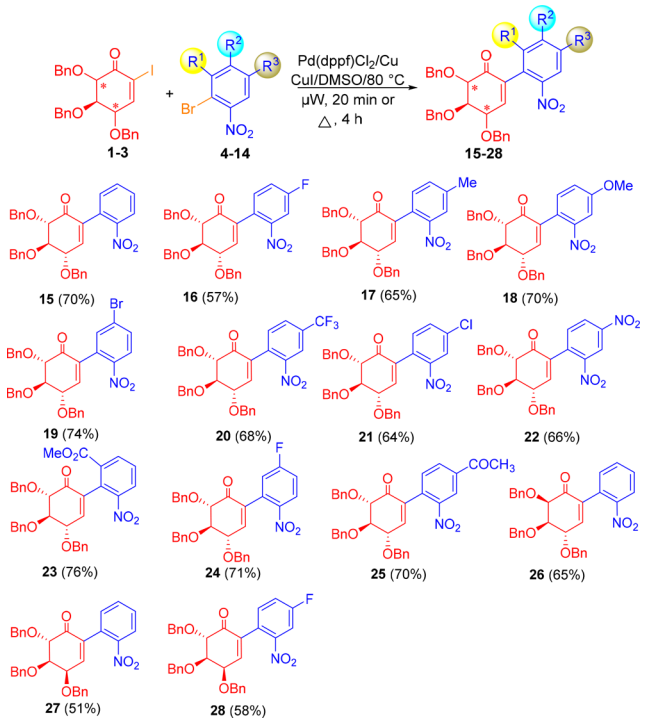
the synthesis of chiral tetrahydrocarbazolones thus remains an attractive challenge.

On the other hand, there are quite a few synthetic methods that have been reported for the synthesis of chiral tetrahydrocarbazoles (CTHCs). Chen and co-workers reported an asymmetric [4 + 2] cycloaddition reaction between α,β-unsaturated aldehydes and *in situ* generated active indole-2,3-quinodimethanes under mild acidic conditions for the synthesis of CTHCs.[13a] Kerr and co-workers developed a $Zn(NTf)_2$ catalyzed [3 + 3] annulative strategy based upon the reaction of donor−acceptor (DA)-cyclopropanes with 2-alkynylindoles for the synthesis of substituted tetrahydrocarbazoles.[13b] Ghorai and co-workers reported a diastereoselective synthesis of functionalized chirally enriched tetrahydrocarbazoles via Lewis acid mediated domino-ring-opening cyclization of donor−acceptor cyclopropanes with 2-vinylindoles.[13c] However, the stereoselective synthesis of polysubstituted chiral tetrahydrocarbazoles remains a highly challenging task.

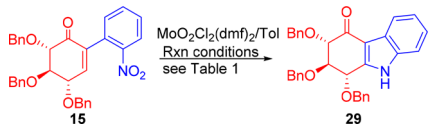
Herein, we disclose a new regioselective synthesis of polysubstituted chirally enriched tetrahydrocarbazolones and carbazoles in one step starting from Ullmann products. The Ullmann products were prepared from commercially available *o*-bromo nitroarenes and readily preparable stereodiverse chiral synthones, α-iodo cyclohexanones **1**−**3** (Scheme 1).

Scheme 1. Synthesis of Ullmann Products 15−28



We planned to transfer natural chirality into our designed tetrahydrocarbazolones. Therefore, we used carbohydrates as chiral synthons. The required α-iodo cyclohexenones **1**−**3** were synthesized from D-glucose, D-galactose, and D-mannose respectively as per the literature.[14] Palladium-catalyzed Ullmann coupling[15] between α-iodo cyclohexenones **1**−**3** and commercially available *o*-bromo nitroarenes **4**−**14** furnished the α-substituted cyclohexenones **15**−**28** in good yield (Scheme 1). We also performed selected Ullmann reactions under microwave conditions, where the reaction was usually complete within 20 min and resulted in the Ullmann product being formed in very good yield. After successful synthesis of the Ullmann products, the next key step attempted was reductive cyclization. The reaction optimization was carried out as summarized in Table 1. We attempted several

Table 1. Reaction Optimization for Synthesis of Tetrahydrocarbazolone 29



entry	reductant[a]	temp (°C)[b]	time	yield (%)
1	none	70	15 min	NR
2	none	90	15 min	NR
3	none	130	15 min	NR
4	PPh_3	70	15 min	traces
5	PPh_3	90	15 min	10
6	PPh_3	130	15 min	60
7	pinacol[c]	130	15 min	50
8	pinacol	130	15 min	70
9	pinacol[d]	130	15 min	65
10[e]	pinacol	130	12 h	60

[a]Reactions were conducted using 5 mol % $MoO_2Cl_2(dmf)_2$ and 4 equiv of reductant. [b]μW heating. [c]2 equiv of reductant used in this case. [d]Dimethylacetamide (DMA) used as solvent. [e]Thermal heating. NR: No reaction.

reductive cyclization conditions (Supporting Information (SI)) on substrate **15**, but these always resulted in a statistical mixture of products, which were difficult to purify and characterize. We therefore looked for new reagents and reaction conditions for arriving at our designed tetrahydrocarbazolone product **29**.

Recent reports have revealed that metal-oxo complexes can be useful reagents in organic synthesis.[16] A plethora of reports are available on MoO_2Cl_2 complexes and their importance in several organic reactions such as oxidation, reduction, catalytic hydrogen transfer, etc.[16a] Among these, catalytic oxo-transfer reactions are a very important process. Fernandes and co-workers reported reduction of pyridine *N*-oxides to pyridine and sulfoxide to sulfide using MoO_2Cl_2 as a catalyst and triethylsilane as a reductant.[16b] Santz and co-workers reported MoO_2Cl_2 catalyzed reductive cyclization of nitro aromatics using PPh_3 toward carbazole preparation.[16c] Later, Santz and co-workers reported several organic transformations, *viz* nitro to amine, sulfoxide to Sulphone, and deoxygenation of heteroaromatic *N*-oxides using pinacol as a reducing agent.[16d] Here, we have developed a new method for the synthesis of chirally enriched tetrahydrocarbazolones using $MoO_2Cl_2(dmf)_2$ as a catalyst and pinacol as a green reductant.

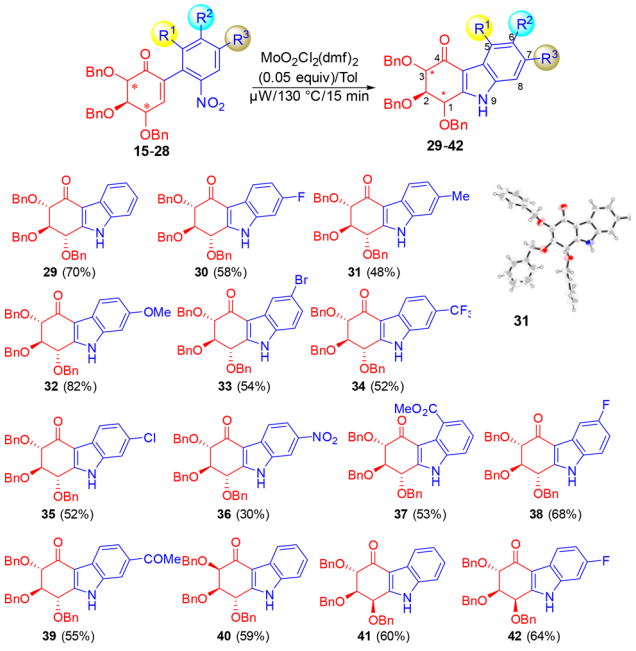
As shown in Table 1, the catalyst $MoO_2Cl_2(dmf)_2$ alone was not sufficient to transform substrate **15** into product **29**, even at high temperature (Table 1, entries 1−3), whereas use of 4 equiv of PPh_3 as a reductant in the same reaction at 130 °C in toluene resulted regioselectively in tetrahydrocarbazolone **29** (60%) within 15 min (Table 1, entry 6). The other possible regioisomer was not seen even by crude ^1H NMR spectroscopy. Use of less equivalents of reductant or a lower temperature decreases the product yield and increases the reaction time, inferring that 4 equiv of reductant and 130 °C temperature are the optimal conditions. We were interested in

DOI: 10.1021/acs.orglett.8b01656
Org. Lett. XXXX, XXX, XXX−XXX

replacing the reductant PPh_3, as it is converted to the corresponding oxide, which was difficult to separate from product **29**. We planned to use pinacol as a reductant, as it gives acetone and water as byproducts, which can be evaporated. After careful screening of the reaction conditions, as shown in Table 1, use of 4 equiv of pinacol and 5 mol % $MoO_2Cl_2(dmf)_2$ catalyst afforded clean regioselective tetrahydrocarbazolone **29** in 70% isolated yield (entry 8) within 15 min under microwave heating at 130 °C in toluene. When we carried out the same transformation in polar solvents such as acetonitrile and DMSO, it did not result in any product, whereas dimethylacetamide furnished product **29** in 65% isolated yield (Table 1, entry 9). This transformation was also feasible at 130 °C but required 12 h (Table 1, entry 10).

After optimization of the reaction conditions for reductive cyclization, we next examined substrate scope for this transformation. We screened several functional groups bearing the stereodivergent substrates **15**–**28**, e.g. fluoro, chloro, bromo, keto, ester, etc., on the aromatic ring, and they were well tolerated and furnished the corresponding tetrahydrocarbazolones **29**–**42** regioselectively in acceptable to very good yields (Scheme 2). Substrates with a nitro group (**22**) or a

Scheme 2. Synthesis of Tetrahydrocarbazolone 29–42

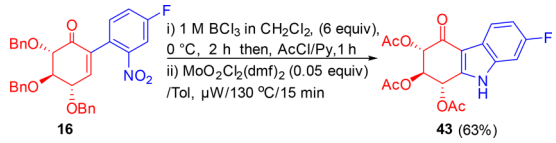


ketone group (**25**) gave product **36** or **39** respectively in lesser yields. We did not observe dehalogenation on halogenated substrates, nor reduction of keto or ester containing substrates. All tetrahydrocarbazolones **29**–**42** were well characterized (SI) including by single crystal X-ray analysis for **31** (Scheme 2).

We next investigated if there is any electronic substituent effect on the chiral carbacycle for this identified transformation. Therefore, electron-withdrawing groups (OAc) were introduced after debenzylation and acetylation on substrate **16** (SI). As shown in Scheme 3, when the resulting tri-*O*-acetyl substrate was treated under the optimized reaction conditions, this furnished tetrahydrocarbazolone **43** in good isolated yield (63%).

The mechanism of this regioselective transformation can be postulated to occur as shown in Figure 2. First the catalyst

Scheme 3. Synthesis of Compound 43



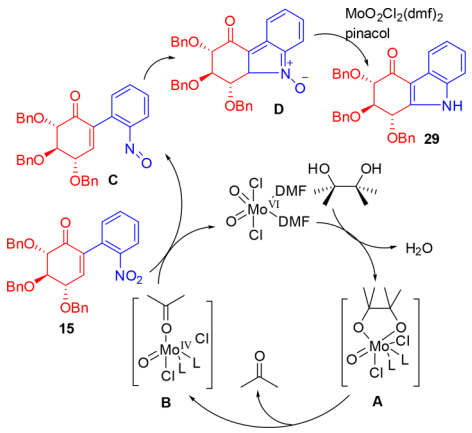


Figure 2. Plausible Mechanism for Tetrahydrocarbazolone Formation.

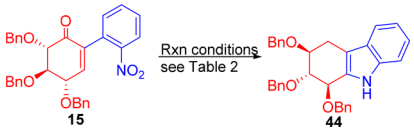
$MoO_2Cl_2(dmf)_2$ reacts with pinacol to form pinacolate complex **A** and water. Pinacolate complex **A** releases acetone to give the molybdenum complex **B**. Oxidative cleavage of the pinacolate by Mo(VI) converts it to Mo(IV) complex **B** and acetone. Then the nitro group in substrate **15** is converted to the nitroso intermediate **C** through oxo group transfer and the oxidation state VI of the molybdenum catalyst is restored. The nitroso intermediate **C** then undergoes 6π electrocyclization resulting in the *N*-oxide intermediate **D**. The catalyst $MoO_2Cl_2(dmf)_2$ and reductant undergo a similar catalytic cycle on intermediate **D** to furnish the tetrahydrocarbazolones **29**.

After successfully obtaining these results, we turned our attention toward synthesis of chiral tetrahydrocarbazoles using the common substrate **15**. Initially, we treated **15** with Zn dust in aqueous NH_4Cl followed by $NaCNBH_3$ in methanol, which furnished tetrahydrocarbazole **44** in 20% yield along with a mixture of products.[17] Fe-catalyzed reductive cyclization in HCl[18] resulted in a complex mixture along with carbazole. In 2003, Banwell and co-workers reported a Pd/C/H_2 gas mediated reductive cyclization.[19a] Later Söderberg and co-workers reported a similar protocol for tetrahydrocarbazole synthesis.[19b] However, Pd/C/H_2 gas mediated reductive cyclization failed on our substrate **15**. Later, we attempted $SnCl_2$ and Pt/C/H_2 conditions, which were also unsuccessful (Table 2, entries 5 and 6). Recently, Banwell and co-workers reported a Raney Ni and H_2 gas mediated reductive annulation reaction for tetrahydrocarbazoles.[19c] When we carried out a Raney Ni mediated reductive annulation on substrate **15** in methanol under H_2 gas, it furnished chirally enriched tetrahydrocarbazoles **44** in 60% isolated yield. This is the first report on preparation of chirally divergent and substituted tetrahydrocarabazoles through a reductive cyclization process.

After having identified and optimized our reaction conditions, we next examined the scope of this reaction for synthesis of substituted tetrahydrocarbazoles. Therefore, we screened differently substituted substrates **15**–**20** on the

DOI: 10.1021/acs.orglett.8b01656
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Reaction Optimization for Synthesis of Tetrahydrocarbazole 44

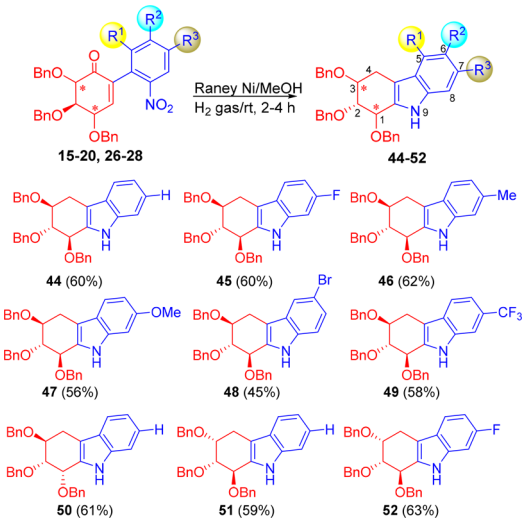


entry	reaction condition	yield[a] (%)
1	Zn dust (8 equiv), NH_4Cl, $NaCNBH_3$, MeOH, rt, 2 h	20
2	Fe powder (5 equiv), 12 N HCl, EtOH/H_2O, 80 °C, 12 h	mix
3	Pd/C, H_2 gas, MeOH, rt, 3 h	NR
4	$SnCl_2$ (5 equiv), EtOH, 80 °C, 2 h	mix
5	Pt/C, MeOH, H_2 gas, rt, 2 h	NR
6	Raney Ni, MeOH, H_2 gas, rt, 3 h	60

[a]Mix: Complex mixture was observed. NR: No reaction.

benzene ring and stereodivergent substrates **26**–**28**. As shown in Scheme 4 they were successfully transformed into products

Scheme 4. Synthesis of Compounds 44–52

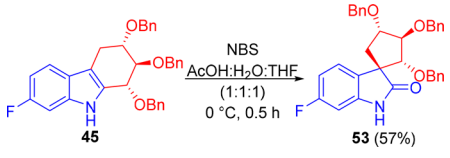


44–**52** in acceptable to good yields. In the case of substrate **19**, debromination was observed and the desired product **48** was obtained in 45% isolated yield.

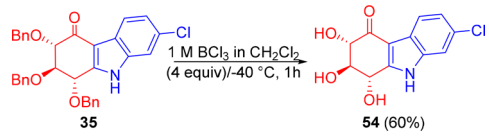
In further explorations, we have transformed chiral tetrahydrocarabazole **45** into the chirally substituted spiro compound **53** using *N*-bromosuccinimide (NBS) in AcOH/H_2O/THF (1:1:1) with a 57% isolated yield (Scheme 5). It is worth mentioning that the spirooxoindoles are privileged scaffolds with ubiquity in numerous natural products and pharmacologically important drugs.[20]

Debenzylation was carried on the substrate **35** using BCl_3 in CH_2Cl_2 at −40 °C, which furnished polyhydroxy substituted chirally enriched tetrahyrocarbazolones **54** in 60% yield (Scheme 6).

Scheme 5. Synthesis of Chiral Spirooxoindole 53

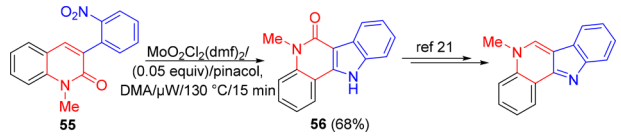


Scheme 6. Debenzylation of 35



Finally, we have shown the synthesis of the methyl derivative of an indoloquinoline alkaloid, cryptosanguinilentine precursor **56**, using this methodology. It possesses antimicrobial and cytotoxic activity. The synthesis started with a palladium catalyzed Suzuki–Miyaura cross-coupling reaction (SI) followed by molybdenum catalyzed reductive cyclization on **55** under optimized reaction conditions (Scheme 7) to afford **56** in 68% isolated yield.

Scheme 7. Synthesis of Natural Product Precursor 56



In summary, we have developed an efficient one-step protocol for the regioselective synthesis of highly functionalized stereodiverse chirally enriched tetrahydrocarabazolones and tetrahydrocarabazoles from a common substrate. The process is catalytic for the synthesis of chirally enriched tetrahydrocarabazolones and requires only 15 min. Mild reaction conditions, operational simplicity, and a green reducing agent are the advantages of this method. The protocol has a wide substrate scope, and electron-donating and -withdrawing groups were well tolerated. We have shown that chirally enriched tetrahydrocarbazole can be transformed into the corresponding spiro product. Furthermore, we have applied this methodology for the synthesis of a cryptosanguinolentine precursor.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01656.

Experimental procedures, reaction optimization conditions, ^1H and ^{13}C NMR spectra, crystallographic data and other supplementary data (PDF)

Accession Codes

CCDC 1586085 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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DOI: 10.1021/acs.orglett.8b01656
Org. Lett. XXXX, XXX, XXX–XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are thankful to the Shiv Nadar University (SNU) for providing required laboratory facilities. C.N. and P.K. are thankful to the Council of Scientific and Industrial Research (CSIR), India for senior research fellowships. The authors are also thankful to the Department of Science and Technology (DST) India for financial support (DST-EMR/2014/000320).

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DOI: 10.1021/acs.orglett.8b01656
Org. Lett. XXXX, XXX, XXX−XXX