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Catalytic Asymmetric Assembly of C3-Monosubstituted Chiral Carbazolones and Concise Formal Synthesis of (−)-Aspidofractinine: Application of Enantioselective Pd-Catalyzed Decarboxylative Protonation of Carbazolones

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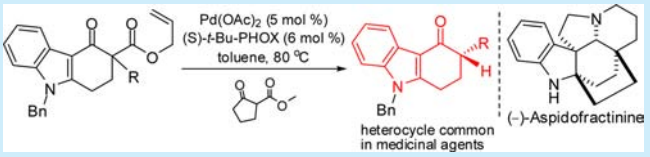
Supporting Information

ABSTRACT: The first method for the asymmetric synthesis of C3-monosubstituted chiral carbazolones, structural motifs common in medicinal chemistry, has been achieved using Pd-catalyzed decarboxylative protonation of carbazolones. This methodology has been applied to the first catalytic enantioselective formal synthesis of (−)-aspidofractinine with step economy and simplicity.



C3-monosubstituted chiral carbazolones **1** (Figure 1) constitute a class of key structural motifs present in

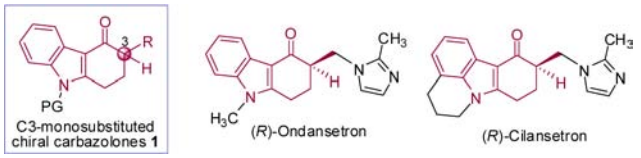


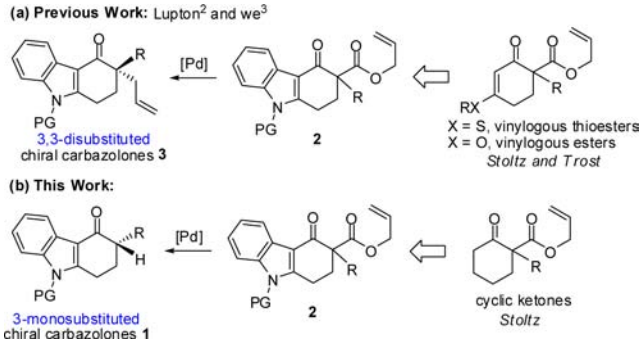
Figure 1. C3-monosubstituted chiral carbazolones **1** and representative drugs containing this motif.

numerous medicinally important agents,[1] for example, (*R*)-Ondansetron. (*R*)-Ondansetron is a synthetic drug used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery.[1a] This drug is also useful for the treatment of behavioral disorders, such as mood anxiety and schizophrenia, and cognitive disorders, such as dementia and senile amnesia.[1b] It is worth noting that (*R*)-Ondansetron is shown to have less adverse effects such as cardiotoxicity than either (*S*)-Ondansetron or racemic Ondansetron.[1c] There has been considerable interest in designing and synthesizing new pharmaceutical compounds containing such motifs.[1d−g] As exemplified in Figure 1, (*R*)-Cilansetron, a drug containing this motif, was designed and synthesized by Solvay Pharmaceuticals Inc. for the treatment of irritable bowel syndrome with diarrhea predominance. (*R*)-Cilansetron is shown to be 7 times more potent than (*S*)-Cilansetron.[1g]

Given the prevalence of C3-monosubstituted chiral carbazolone motifs in medicinal chemistry and the importance of their C3-absolute configuration, the development of an enantioselective method to generate this functionality is highly desirable. However, asymmetric synthesis C3-monosubstituted chiral carbazolones has not yet been achieved so far. The preparation of C3-monosubstituted chiral carbazolones relies on racemic synthesis followed by subsequent chiral resolution. Hence, we became interested in addressing this important but unmet synthetic issue.

Very recently, Lupton[2] and we[3] concurrently reported the enantioselective Pd-catalyzed decarboxylative allylation of carbazolones **2**, and C3-*disubstituted* chiral carbazolones **3** were obtained in good yields and enantioselectivities (Scheme 1a). Inspired by this study, we envisioned that enantioselective

Scheme 1



Pd-catalyzed decarboxylative protonation of carbazolones **2**, if successful, could offer direct access to C3-*monosubstituted* chiral carbazolones **1**. Herein we report the realization of the first asymmetric synthesis of C3-monosubstituted chiral carbazolones **1** by using Pd-catalyzed decarboxylative protonation of carbazolones (Scheme 1b). The utility of carbazolones **1** in the context of natural product synthesis has been demonstrated by

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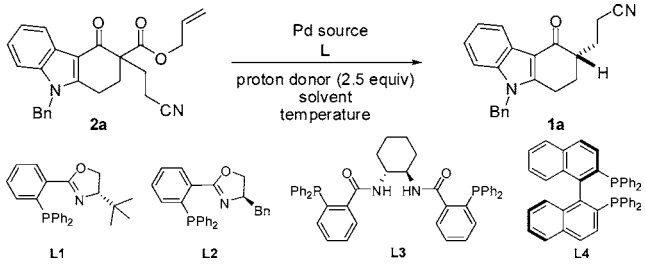
the completion of the first catalytic enantioselective formal synthesis of (−)-aspidofractinine with step economy and simplicity.

Although Pd-catalyzed decarboxylative protonation[4] of carbazolones has not yet been reported, the transformations of related cyclic ketones are known,[5,6] especially with Stoltz's contribution.[7] We postulated that carbazolones as a new class of protonation substrates should behave as vinylogous amides;[8] thus appropriate indole *N*-protection should allow the proposed protonation reaction to occur. Hence, we commenced this study.

When *N*-benzyl-protected carbazolone **2a** was subjected to the heterogeneous conditions developed by Stoltz,[7a] namely $Pd(OAc)_2$, the PHOX ligand **L1**,[9] HCO_2H, and 4 Å molecular sieves at 40 °C, no protonation reaction was observed. Heating to 80 °C still did not lead to the protonation reaction to occur. When carbazolone **2a** was subjected to the homogeneous conditions reported by Stoltz,[7b] namely $Pd_2(dba)_3$, **L1**, and Meldrum's acid at 23 °C, no reaction occurred. However, heating to 80 °C provided protonated product **1a**. Unfortunately, almost no enantioselectivity was observed (Table 1, entry 1). Interestingly, the solvents were found to have significant effects on the enantioselectivity of this protonation reaction. When the reaction was performed in toluene instead of 1,4-dioxane (at 80 °C), the enantioselectivity was remarkably improved (76% ee, entry 2 versus 1). Then the effects of temperature on the enantioselectivity were investigated, and 80 °C was determined to be still optimal. In an effort to improve the enantioselectivity, a series of other organic proton donors were screened. Unfortunately, they all provided **1a** in lower ee than the Meldrum's acid case (see Supporting Information for details). A screen of alternative chiral ligands revealed that the PHOX ligand **L1** gave the best results (entries 6−8 versus 2). Finally, the effects of Pd sources on this protonation reaction were examined. The use of $Pd(OAc)_2$ (with Meldrum's acid as proton donor) led to a significant improvement in yield, but the enantioselectivity dropped dramatically (entry 9). This observation led us to rescreen proton donors (with $Pd(OAc)_2$ as the Pd source) (see Supporting Information for details). Pleasingly, the use of methyl 2-cyclopentanonecarboxylate as the proton donor provided C3-monosubstituted carbazolone **1a** in excellent yield (92%) with high enantioselectivity (92% ee) (entry 10).

Table 1. Optimization of Protonation Reaction of Carbazolone 2a

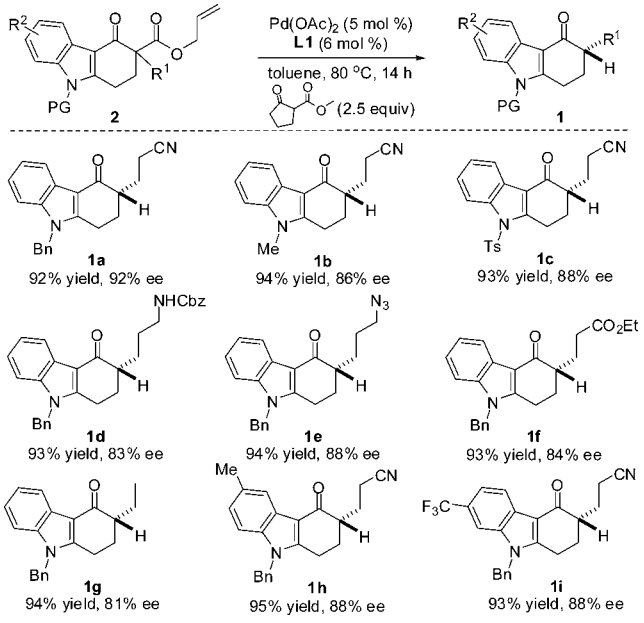


entry	Pd source	L	proton donor	temp (°C)	solvent	yield (%)[a]	ee (%)[b]
1[c]	$Pd_2(dba)_3$	L1		80	dioxane	87	4
2[c]	$Pd_2(dba)_3$	L1		80	toluene	69	76
3[c]	$Pd_2(dba)_3$	L1		80	*m*-xylene	63	58
4[c]	$Pd_2(dba)_3$	L1		70	toluene	62	51
5[c]	$Pd_2(dba)_3$	L1		90	toluene	70	55
6[c]	$Pd_2(dba)_3$	L2		80	toluene	70	-27
7[c]	$Pd_2(dba)_3$	L3		80	toluene	68	0
8[c]	$Pd_2(dba)_3$	L4		80	toluene	67	0
9[d]	$Pd(OAc)_2$	L1		80	toluene	92	55
10[d]	$Pd(OAc)_2$	L1		80	toluene	92	92
11[d]	$Pd(TFA)_2$	L1		80	toluene	66	14

[a]All reactions were performed with 0.073 mmol of racemic **2a** at 0.027 M (14 h). [b]Determined by chiral HPLC analysis. [c]$[Pd_2(dba)_3]$ (5 mol %), **L** (12 mol %). [d]$Pd(OAc)_2$ or $Pd(TFA)_2$ (5 mol %), **L** (6 mol %).

The present protonation reaction serves as a general method for the enantioselective synthesis of C3-monosubstituted chiral carbazolones. As shown in Scheme 2, a variety of C3-monosubstituted chiral carbazolones **1** bearing various useful functionalities such as CN, CO_2Et, NHCbz, and N_3 were accessed in excellent yields (92−95%) with good enantioselectivities (81−92% ee) when the optimized reaction conditions were used. Changing from *N*-benzyl to *N*-methyl and *N*-Ts protection was also well tolerated. Furthermore, the substrates with different substituents on the benzene ring also afforded the desired products **1h** and **1i** in excellent yields with high enantioselectivities. Finally, it is worth pointing out that the enantiomers of C3-monosubstituted chiral carbazolones **1** should also be obtained by the corresponding Pd-catalyzed decarboxylative protonation of carbazolones **2** because of the availability of the *ent*-**L1** ligand.

Scheme 2. General Enantioselective Synthesis of C3-Monosubstituted Chiral Carbazolones 1



The synthetic application of this method in the context of natural product synthesis was demonstrated by the completion of the first catalytic enantioselective formal synthesis of

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(−)-aspidofractinine (Figure 2), a complex indole alkaloid which is characterized by a caged and strained hexacyclic architecture with quaternary centers at C-2, C-7, and C-20.

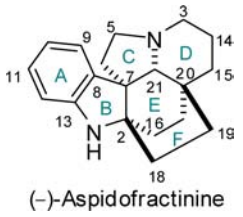
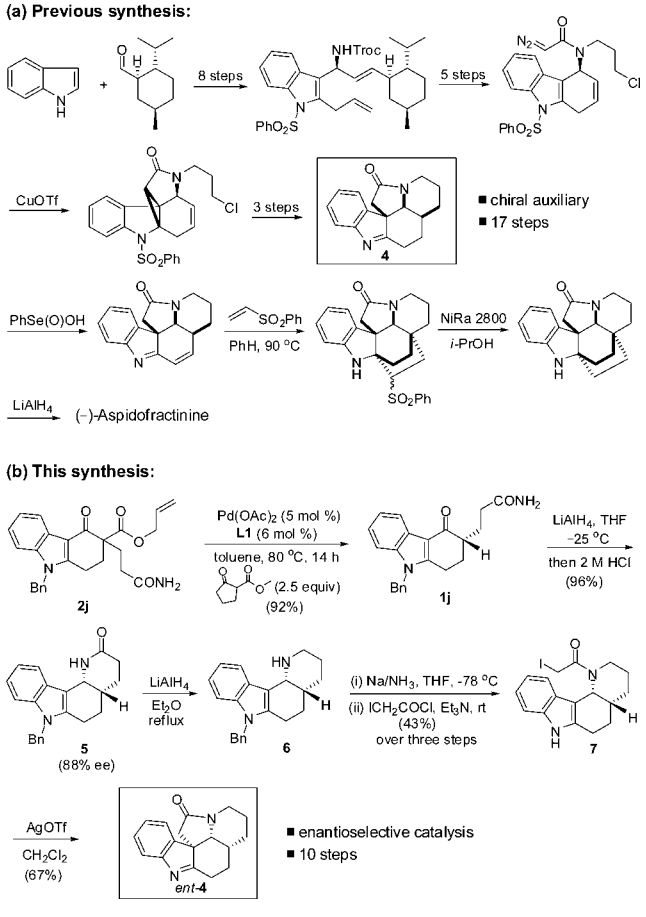


Figure 2. Structure of (−)-aspidofractinine.

Although the first total synthesis of aspidofractinine was achieved by Ban in 1976, who obtained aspidofractinine as a racemic mixture,[10a] to date there is only one report of the synthesis of optically active (+)-aspidofractinine,[11] implying that there are some asymmetric synthetic challenges posed by this cage-like target. This elegant synthesis of (+)-aspidofractinine using *p*-menthyl-3-carboxaldehyde as a chiral auxiliary required 17 steps to produce the key pentacyclic intermediate **4**, which was subsequently transformed into (+)-aspidofractinine in 4 steps (Scheme 3a).[11] To the best of our knowledge, to date there is no report of catalytic enantioselective synthesis of aspidofractinine. We envisioned that Pd-catalyzed enantioselective decarboxylative protonation of carbazolones would provide a suitable framework for a concise, distinct approach toward the synthesis of (−)-aspidofractinine featuring enantioselective catalysis.

Scheme 3



As shown in Scheme 3b, under our protonation reaction conditions, the enantioselective decarboxylative protonation of carbazolone **2j**[12] proceeded smoothly to give the desired C3-monosubstituted carbazolone **1j** in 92% yield; however, its ee value could not be determined by chiral HPLC. Thus, carbazolone **1j** was transformed into lactam **5**. Fortunately, the ee value of **5** could be easily determined (88% ee). Then reduction of the amide group with $LiAlH_4$, *N*-debenzylation with Na/NH_3, and acylation with 2-iodoacetyl chloride afforded amide **7**. **7** was treated with AgOTf to produce the key intermediate *ent*-**4**. The NMR data of *ent*-**4** were in accordance with those reported,[11] thus constituting the first catalytic enantioselective formal synthesis of (−)-aspidofractinine. It is worth noting that this synthesis only required a total of 10 steps from commercially available starting materials.

In summary, we have achieved the first method for the general enantioselective synthesis of C3-monosubstituted chiral carbazolones, key structural motifs in medicinal chemistry, by using Pd-catalyzed decarboxylative[13] protonation of carbazolones. The synthetic application of this methodology was demonstrated in the context of natural product synthesis. A key pentacyclic intermediate, en route to the synthesis of natural (−)-aspidofractinine, has been prepared in only 10 steps from commercially available starting materials (17 steps for the previous chiral auxiliary approach[11]). Our synthesis not only constitutes the first catalytic enantioselective approach to aspidofractinine but also represents the first reported application of Pd-catalyzed enantioselective decarboxylative protonation reactions in the synthesis of a complex natural product.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and copies of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Richard, J. *Drugs* **1991**, *41*, 574. (b) Young, J. W. Int. Appl. PCT, WO 1993000074 A1, 1993. (c) Bodhankar, S. L.; Thakurdesai, P. A.; Maurya, O. P. *Pharmacologyonline* **2006**, *3*, 153. (d) Elz, S.; Heil, W. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 667. (e) Romeo, G.; Materia, L.; Pittala, V.; Modica, M.; Salerno, L.; Siracusa, M.; Russo, F.; Minneman, K. P. *Bioorg. Med. Chem.* **2006**, *14*, 5211. (f) Georg, S.

dx.doi.org/10.1021/ol501877x | *Org. Lett.* 2014, 16, 4178−4181

Expert Rev. Gastroenterol. Hepatol. **2007**, *1*, 15. (g) van Wijngaarden, I.; Hamminga, D.; van Hes, R.; Standaar, P. J.; Tipker, J.; Tulp, M. T. M.; Mol, F.; Olivier, B.; de Jonge, A. *J. Med. Chem.* **1993**, *36*, 3693.
(2) Gartshore, C. J.; Lupton, D. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113.
(3) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117.
(4) For reviews on enantioselective protonation, see: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359. (b) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. (c) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1. (d) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. (e) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis, Supplement 2*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; pp 125−132. (f) Blanchet, J.; Baudoux, J.; Amere, M.; Lasne, M.-C.; Rouden, J. *Eur. J. Org. Chem.* **2008**, 5493. (g) Claraz, A.; Oudeyer, S.; Levacher, V. *Curr. Org. Chem.* **2012**, *16*, 2192. (h) Nakamura, S. *Org. Biomol. Chem.* **2014**, *12*, 394. (i) Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, DOI: 10.1002/ejoc.201402213.
(5) The first nonenantioselective Pd-catalyzed decarboxylative protonation has been reported by Tsuji, see: (a) Tsuji, J.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1985**, *50*, 3416. (b) Mandai, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 5395.
(6) (a) Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1161. (b) Aboulhoda, S. J.; Hénin, F.; Muzart, J.; Thorey, C.; Behnen, W.; Martens, J.; Mehler, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1321. (c) Abouldoda, S. J.; Letinois, S.; Wilken, J.; Reiners, I.; Hénin, F.; Martnes, J.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1865. (d) Baur, M. A.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2755.
(7) (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039.
(8) A review on the role of vinylogy in reaction discovery: Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.
(9) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336 and references therein.
(10) Racemic syntheses: (a) Ban, Y.; Homna, Y.; Oishi, T. *Tetrahedron Lett.* **1976**, *14*, 1111. (b) Ban, Y.; Ohnuma, T.; Oishi, T.; Kinoshita, H. *Chem. Lett.* **1986**, 927. (c) Cartier, D.; Ouahrani, M.; Lévy, J. T. *Tetrahedron Lett.* **1989**, *30*, 1951. (d) Dufour, M.; Gramain, J. C.; Husson, H. P.; Sinibaldi, M. E.; Troin, Y. *Tetrahedron Lett.* **1989**, *30*, 3429. (e) Wenkert, E.; Liu, S. *J. Org. Chem.* **1994**, *59*, 7677.
(11) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, *74*, 6035.
(12) Compound **2j** was prepared in four steps from commercially available 1,2,3,9-tetrahydro-4*H*-carbazol-4-one. See Supporting Information for details.
(13) (a) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. (b) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138.