Multiple Hydrogen-Bonding Bifunctional Thiourea-Catalyzed Asymmetric Dearomative [4 + 2] Annulation of 3-Nitroindoles: Highly Enantioselective Access to Hydrocarbazole Skeletons

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Supporting Information

ABSTRACT: A method for the enantioselective construction of hydrocarbazole skeletons through dearomative [4 + 2] annulation of 3-nitroindoles with Nazarov reagents is reported. The reactions use multiple hydrogen-bonding bifunctional thiourea as catalyst and are highly diastereo- and enantioselective (up to >20:1 dr and >99% ee). The protocol was demonstrated by preparative-scale experiment and the versatile conversion of the products. The multiple hydrogen-bonding in the catalyst plays a pivotal role in the reactivity and stereoselectivity.

Development of efficient and highly stereoselective strategies to achieve promising chiral molecules, containing biologically relevant structures, is a continuing challenge in synthetic chemistry. Chiral hydrocarbazoles, possessing a heterotricyclic indoline system, have been found to be core elements commonly present in a wide range of biologically active natural products and pharmaceuticals (Figure 1).1 Stereocontrolled synthesis of chiral hydrocarbazole derivatives has attracted considerable attention from synthetic and medicinal chemists.2 Some unique approaches for the construction of the chiral hydrocarbazole frameworks have been reported.2,3 However, because a defined three-dimensional shape of chiral molecules greatly influences their biological activities, a more efficient and accessible methodology toward the construction of hydrocarbazole skeletons with high stereoselectivity is still highly in demand.

Recently, dearomative cycloaddition reaction has emerged as one of the simple and powerful strategies to access polycyclic compounds from readily available starting materials.4 In this realm, N-substituted 3-nitroindoles,5 which are a particular type of electron-deficient indoles possessing two electron-withdrawing groups at N1 and C3 positions,6 have demonstrated their potential in the construction of polycyclic structures via a dearomative cycloaddition process.7−9 Several groups have reported the asymmetric cycloaddition reactions of 3-nitroindoles with metal catalysis8 or organocatalysis.9 Generally, 3-nitroindoles are inclined to undergo nucleophilic addition at the C2 position, and sequentially, electrophilic functionalization takes place at the C3 position (Scheme 1). We noticed that the

Scheme 1. Reactivity of 3-Nitroindoles and Synthetic Strategy for the Construction of Hydrocarbazole Skeletons

Received: July 7, 2017
Published: August 15, 2017
Nazarov reagents, which possess a nucleophilic α-carbon and an electronically deficient C=C double bond, were commonly used in annulation reactions to build up a cyclohexenone moiety. In this context, we envisioned that hydrocarbazole skeletons with three continuous stereocenters could be constructed through dearomative [4 + 2] annulation between 3-nitroindoles and Nazarov reagents controlled by a suitable chiral catalyst (Scheme 1).

Application of chiral multiple hydrogen-bonding bifunctional thiourea organocatalysts for the synthesis of enantiomerically enriched molecules has attracted more and more attention from the organocatalytic community. The bifunctional nature of these types of catalysts, dual activation, which includes the activation of the acceptors by the hydrogen-bonding of the thiourea group and the simultaneous activation of the donors by the tertiary amine group, is crucial for the reactivity and stereocontrol. As a continuation of our studies on the reaction of 3-nitroindoles and development of new methodologies with asymmetric organocatalysis, we present a highly efficient strategy catalyzed by a multiple hydrogen-bonding bifunctional thiourea for enantioselective construction of hydrocarbazole skeletons through dearomative [4 + 2] annulation of 3-nitroindoles with Nazarov reagents, giving the chiral hydrocarbazole derivatives in good to excellent yields with excellent diastereo- and enantioselectivities (up to 97% yield, >20:1 dr, and >99% ee) and with significant opportunities for structural diversification.

We initiated our studies with the reaction of 3-nitroindole 1a and Nazarov reagent 2a in CH2Cl2 at room temperature (Table 1). The reaction was complete with 20 mol % of bifunctional thiourea catalyst A in 48 h and furnished 3a in 97% yield with >20:1 dr and −67% ee (entry 1). To facilitate chiral HPLC analysis, the original product was acetylated to 3a. Catalysts B and C could catalyze the reaction just as catalyst A in reactivity and diastereoselectivity, but with significantly decreased ee values (entries 2 and 3). Application of catalyst D, bearing multiple hydrogen-bonding donors, gave 3a in 68% yield with >20:1 dr and 79% ee (entry 4). Multiple hydrogen-bonding thiourea catalyst E was able to furnish 3a in 95% yield with 16:1 dr and 82% ee (entry 5). Afterward, the solvent screening (entries 6–9) revealed CHCl3 is the best solvent (entry 7). Adding 100 mg of 4 Å molecular sieves into the reaction mixture resulted in slightly higher dr and ee (entry 10). When temperature was decreased to 0 °C, comparable yield and dr value were obtained and up to 93% ee was observed (entry 11). Ultimately, the further improved enantioselectivity, excellent yield, and diastereoselectivity could be obtained with even lower temperature, but an extended reaction time was required (entry 12). The absolute configuration of 3a was determined to be (CSS,C6S,C7R) by single-crystal X-ray diffraction analysis.

With the optimized reaction conditions established, various 3-nitroindoles were tested by reacting with 2a (Scheme 2), the reactivity and stereoselectivity were hardly affected by the incorporation of electron-withdrawing in the N1 position of 3-nitroindoles as 86–97% yields and excellent dr and ee values were observed for products 3b–g. Moreover, substrates with an electron-withdrawing or electron-donating substituent at the aromatic ring of 3-nitroindoles were suitable for this catalytic transformation, affording the desired products in virtually pure stereoisomers with very high yields (3h and 3i). However, the N-Me 3-nitroindole or N-H 3-nitroindole did not react with 2a under the standard reaction conditions (3j), probably due to the electron-rich property, resulting in the low reactivity for the substrate.

### Table 1. Optimization Conditions

| Entry | Catalyst | Solvent | t (°C) | Yield (%) | dr | ee (%) |
|-------|----------|---------|--------|-----------|----|--------|
| 1     | A        | CH2Cl2  | rt     | 97        | >20:1 | −67    |
| 2     | B        | CH2Cl2  | rt     | 96        | >20:1 | 47     |
| 3     | C        | CH2Cl2  | rt     | 93        | >20:1 | 33     |
| 4     | D        | CH2Cl2  | rt     | 68        | >20:1 | 79     |
| 5     | E        | CH2Cl2  | rt     | 95        | 16:1  | 82     |
| 6     | E        | Cl(CH2)2Cl | rt     | 95        | 19:1  | 81     |
| 7     | E        | CHCl3   | rt     | 98        | 13:1  | 86     |
| 8     | E        | toluene | rt     | 97        | >20:1 | 83     |
| 9     | E        | CH,CN   | rt     | 98        | 9:1   | 64     |
| 10    | E        | CHCl3   | rt     | 95        | >20:1 | 81     |
| 11    | E        | CHCl3   | 0      | 95        | >20:1 | 93     |
| 12    | E        | CHCl3   | −10    | 95        | >20:1 | 95     |

*Unless noted, reactions were carried out with 1a (0.1 mmol), 2a (0.2 mmol), and 20 mol % of catalyst in 0.5 mL of solvent at room temperature for 48 h (see Supporting Information for experimental details). Isolated yields. *Determined by chiral HPLC analysis. 100 mg 4 Å MS was used. Reaction time was 72 h.

### Scheme 2. Substrate Scope of 3-Nitroindoles

See Supporting Information for experimental details. Isolated yields. *Determined by 1H NMR analysis of the crude mixture. Determined by chiral HPLC analysis; n.r. = no reaction.
Next, a variety of Nazarov reagents were examined by reacting with 3-nitroindole 1g (Scheme 3). By installing an electron-withdrawing or electron-donating group into the aromatic ring of Nazarov reagents, regardless of their position at the phenyl ring, the Nazarov reagents could react smoothly with 1g and furnish their respective annulation products with excellent results (3k-q). Heteroaromatic Nazarov reagents were also successfully employed in the asymmetric dearomative [4 + 2] annulation reaction under the same conditions, generating 3r and 3s in excellent yields and dr and ee values. Additionally, the naphthyl moiety was also tolerated in the annulation reaction and led to 3t in excellent results. The reaction also had a good tolerance for the Nazarov reagents with different ester groups, and a set of satisfactory results could be obtained for 3u and 3v.

Unfortunately, the aliphatic substrate of Nazarov reagents could not react with 1g under the standard reaction conditions (data not shown).

To demonstrate the preparative utility of this methodology, reaction of 1a and 2a was performed on a gram scale with catalyst E (Scheme 4). Under the optimized conditions, the reaction proceeded very well and directly provided the tetrahydrocarbazole-type product 4 in 97% yield with >20:1 dr and 96% ee. The dr and ee values of 4 could be readily upgraded to >20:1 dr and 98% ee via a recrystallization from the mixture of CH2Cl2 and petroleum ether (v/v 1:5). Nevertheless, the gram scale reaction smoothly gave corresponding acetylated product 3a in 97% yield without any loss of stereoselectivities. Moreover, almost complete diastereo- and enantioselectivities for 3a could be realized through a simple recrystallization operation.

To further demonstrate the synthetic value of this work, we explored several promising derivatizations to the products (Scheme 5).13 Treating product 4 with NaBH4 in EtOH at 0°C for 1 h afforded the monohydroxyl 5 in 92% yield, >20:1 dr, and 98% ee. However, the same reduction reaction was carried out at 0°C for 1 h and then at room temperature for 24 h, providing dihydroxyl 6 in 88% yield. Treating compound 6 with TsOH in acetone could furnish acetonide product 7 in 80% yield. Notably, there was no loss in the optical purity during the two-step transformations from 4 to 7. Reacting 4 with NBS in CH2Cl2 gave brominated product 8 in 95% yield with >20:1 dr and 97% ee. The nitro group in 3a could be readily reduced to an amino group with active zinc dust, giving 9 with excellent results.

To gain insight into the pivotal role of the multiple hydrogen-bonding bifunctional thiourea catalyst E, some comparative experiments were carried out using different catalysts (Scheme 6). Under the optimal conditions, E efficiently catalyzed the reaction and gave 3a in 95% yield, >20:1 dr, and 95% ee. However, with catalyst B, 3a was obtained in 89% yield, >20:1 dr, and 64% ee. Comparison of these two reactions suggested that...
the 1-phenylalanine scaffold in E is important for the reactivity and enantioselectivity. Then, using F as catalyst, the reaction afforded 3a only in a trace amount. This result revealed the hydrogen-bonding of the amide group in the catalyst plays a vital role in the reactivity. Ultimately, catalyst G furnished 3a in only 13% yield and 6% ee, albeit with >20:1 dr. We could infer that the thiourea group of E is crucial for the reaction. Therefore, it can be readily concluded that the multiple hydrogen-bonding in the catalyst was distinctly important to the high reactivity and excellent dr and ee values of the asymmetric dearomative \([4+2]\) annulation process.

In summary, we have realized the first catalytic asymmetric dearomative \([4+2]\) annulation of 3-nitroindoles with Nazarov reagents. With a multiple hydrogen-bonding bifunctional thiourea catalyst, a wide range of optically active hydrocarbazole derivatives can be obtained in high yields (up to 97% yield) with excellent diastereo- and enantioselectivities (up to >20:1 dr and >99% ee). The reaction displays a general scope for both 3-nitroindoles and Nazarov reagents. The usefulness of the protocol was also demonstrated by the preparative-scale annulation process.

**ACKNOWLEDGMENTS**

(1) (a) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 1–197. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* 2002, 102, 4303.

(2) (a) Bonjoch, J.; Solé, D. *Chem. Rev.* 2000, 100, 3455. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* 2011, 44, 447. (c) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *Angew. Chem., Int. Ed.* 2015, 54, 400.

(3) (a) Andrews, I. P.; Kwon, O. *Chem. Sci.* 2012, 3, 2510. (b) 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, 6015. (c) Shen, X.-L.; Zhao, R.-R.; Mo, M.-J.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* 2014, 79, 2473.

(4) (a) Andrade, M.; Ruiz, F.; Feuerstein, M.; Marque, S. R. A.; Santelli, M. *Tetrahedron* 2013, 69, 8325. (b) Zhou, J.-Q.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* 2015, 17, 5020. (c) Gerten, A. L.; Stanley, L. M. *Org. Chem. Front.* 2016, 3, 339.

(5) (a) Gérard, H.; Chataigner, I. *J. Org. Chem.* 2013, 78, 9233. (b) Andreini, M.; Chapellas, F.; Diab, S.; Pasturaud, K.; Piettre, S. R.; Legros, J.; Chataigner, I. *Org. Biomol. Chem.* 2016, 14, 2833. (c) Liu, X.; Yang, D.; Wang, K.; Zhang, J.-Q.; Wang, R. *Green Chem.* 2017, 19, 8226. (d) Rivinoja, D. J.; Gee, Y. S.; Gardiner, M. G.; Ryan, J. H.; Hyland, C. J. T. *Angew. Chem., Int. Ed.* 2017, 56, 1053. (e) Liao, J.; Chertov, O.; Fokin, V. V.; Ratovelomanana-Vidal, V.; Vitale, M. *R. Org. Lett.* 2017, 19, 2238. (f) Ananthan, P. V.; Babu, S. A.; Krishnan R. A.; Suresh, E.; John, J. *Org. Lett.* 2017, 19, 2458.

(6) (a) Pape, A. R.; Kalappan, K. P.; Kündig, E. *Chem. Rev.* 2000, 100, 2917. (b) Zu, C.-J.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* 2012, 51, 12662. (c) Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res.* 2014, 47, 2558.

(7) For the synthesis of 3-nitroindoles, see: (a) Pelkey, E. T.; Gribble, G. W. *Synthesis* 1999, 1117. (b) Nowrouzi, N.; Mohrenpour, A. M.; Bashiri, E.; Shayan, Z. *Tetrahedron Lett.* 2012, 53, 4841.

(8) (a) Chataigner, I; Panell, C.; Gérard, H.; Piettre, S. R. *Chem. Commun.* 2007, 3288. (b) Chataigner, I; Piettre, S. R. *Org. Lett.* 2007, 9, 4159. (c) Lee, S.; Chataigner, I; Piettre, S. R. *Angew. Chem., Int. Ed.* 2011, 50, 472. (d) Lee, S.; Diab, S.; Queval, P.; Sebban, M.; Chataigner, I; Piettre, S. R. *Chem. - Eur. J.* 2013, 19, 7181. (e) Beemelmans, C.; Gross, S.; Reissig, H.-U. *Chem. - Eur. J.* 2013, 19, 17801.

(9) For a review on Nazarov reagents in organic synthesis, see: (a) Andreini, M.; De Paolis, M.; Chataigner, I. *Catal. Commun.* 2015, 63, 15. (b) Zhao, J.-Q.; Zhou, M.-Q.; Wu, Z.-J.; Wang, Z.-H.; You, S.-F.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* 2015, 17, 5020. (c) Gerten, A. L.; Stanley, L. M. *Org. Chem. Front.* 2016, 3, 339.

(10) For a review on reagents in organic synthesis, see: (a) Multani, P.; Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* 2015, 51, 1810. (b) Guo, Y.; Zeng, C.; Han, X.-J.; Qu, H.; Zhao, X.-H.; An, X.-T.; Fan, C.-A. *J. Am. Chem. Soc.* 2015, 137, 4267.

(11) For selected reviews of bifunctional thiourea catalysis, see: (a) Takemoto, Y. *Org. Biomol. Chem.* 2005, 3, 4299. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* 2007, 107, 5713. (c) Yu, X.; Wang, W. *Chem. - Asian J.* 2008, 3, 516. (d) Zhang, Z.; Schreiner, P. R. *Chem. Rev.* 2009, 108, 1187. (e) Fang, X.; Wang, C.-J. *Chem. Commun.* 2015, 51, 1185. (f) Okino, T.; Hossishi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* 2003, 125, 12672. (g) Nakamura, Y.; Yamauchi, M.; Yamashita, K.; Ohmori, T.; Gortler, C.; Sorokin, I. *Org. Lett.* 2002, 4, 2665. (h) McCooey, S. H.; Conner, S. N. *Angew. Chem., Int. Ed.* 2004, 43, 6367. (i) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* 2005, 4481. (j) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* 2008, 130, 14416. (k) Zhou, Q.; Lu, Y. *Angew. Chem., Int. Ed.* 2010, 49, 7753. (l) Dou, X.; Lu, Y. *Chem. - Eur. J.* 2012, 18, 9315. (m) Luo, J.; Wang, H.; Zhong, F.; Kwiatkowski, F.; Xu, L.-W.; Lu, Y. *Chem. Commun.* 2013, 49, 5775. (n) Dou, X.; Yao, W.; Zhou, B.; Lu, Y. *Chem. Commun.* 2013, 49, 9224.

(12) (a) Zhang, M.-L.; Wu, Z.-J.; Zhao, J.-Q.; Luo, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* 2016, 18, 5110. (b) Wang, Z.-H.; Wu, Z.-J.; Yue, D.-F.; Hu, W.-F.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *Chem. Commun.* 2016, 52, 11708.

(13) See Supporting Information for more details.

(14) CCDC 1460783 (3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.