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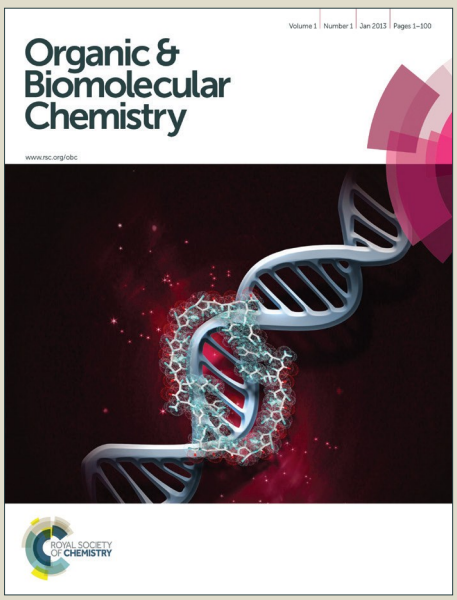

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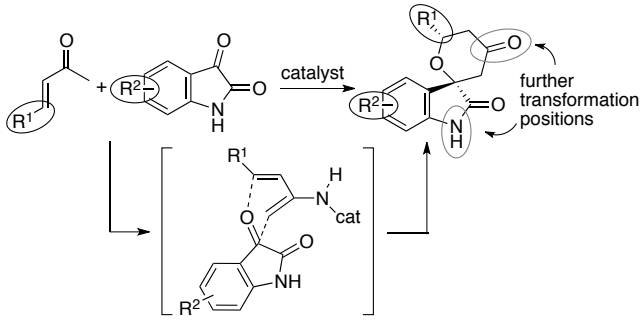
Catalytic Asymmetric Hetero-Diels-Alder Reactions of Enones with Isatins to Access Functionalized Spirooxindole Tetrahydropyrans: Scope, Derivatization, and Discovery of Bioactives

Hai-Lei Cui, Pandurang V. Chouthaiwale, Feng Yin, and Fujie Tanaka*[a]

Abstract: The development of concise methods for the synthesis of functionalized small molecules is important in the search of new bioactive molecules. To contribute to this, we have developed oxa-hetero-Diels-Alder reactions of enones with isatins catalyzed by amine-based catalyst systems. Various spirooxindole tetrahydropyranones were synthesized either in enantiomerically enriched forms or as racemic forms depending on the catalyst system. The reaction products were further transformed at the ketone carbonyl group and the indole nitrogen. Using these reactions, functionalized spirooxindole tetrahydropyran derivatives with functional groups in four directions in three-dimensional space were concisely obtained. From these synthesized compounds, an inhibitor of human ion channel Nav1.7 with μM-level activity was identified, indicating that the developed reaction methods are useful for providing molecules for the discovery of new biofunctional molecules.

Introduction

The development of concise methods for the synthesis of series of functionalized small molecules is important in the search of new bioactive molecules.[1] The desired reaction methods for these purposes should accept a wide range of reactants to generate various product compounds, yet should provide the desired products with high selectivities. Optimally, these reactions should be performed under safe, mild conditions. To address these points, we have recently developed hetero-Diels-Alder (hDA) reactions of enones with isatins catalyzed by amine-based catalyst systems that provide spirooxindole tetrahydropyranones under mild conditions (Scheme 1); the initial results have been reported as a communication.[2] We have also reported mechanistic investigation of the reactions catalyzed by the amine-based three-component catalyst systems.[3] Here we report expansion of the scope of the hDA reactions, derivatization of the hDA reaction products, and the use of the molecules synthesized by the hDA reaction methods for identification of biofunctional molecules.



Scheme 1. The hetero-Diels Alder reactions catalyzed by amine-based catalysts.

Results and Discussion

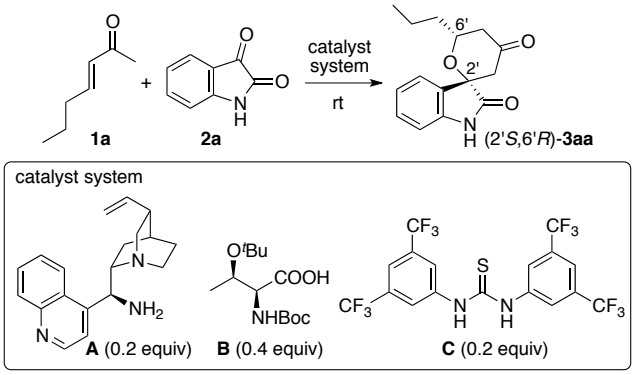
1. Hetero-Diels-Alder reactions of enones with isatins

Spirooxindole cores are present in many bioactive molecules.[4] Although a number of spirooxindole cores have been synthesized,[2-7] efficient methods for the synthesis of tetrahydropyran-derived spirooxindoles had not been reported until our recent communication.[2]

We reasoned that the spirooxindole tetrahydropyran core would be a useful molecular scaffold if these compounds could be easily synthesized. We designed and optimized hDA reactions of enones with isatins catalyzed by amine-based catalysts to concisely access to spirooxindole tetrahydropyranones (Scheme 1).[2,3] This method should allow concise access to various hDA products when substituted enones and isatins are used as reactants. In addition, in our design, the hDA reactions can be performed without the need of protection of the isatin nitrogen[2] and the hDA reaction products can be used for further functionalization at the ketone carbonyl group and the indole nitrogen (Scheme 1). With substitutions on enones and isatins and with the derivatization at the ketone and the isatin nitrogen, functional groups will point in four directions from the spirooxindole tetrahydropyran core; this structural feature may be useful for the search of biofunctional molecules.

Enamine activation of enones in situ has been demonstrated in many reactions including cycloadditions to form all-carbon 6-membered products and nitrogen-containing 6-membered products.[8,9,10] However, formation of tetrahydropyranones via the reactions of in situ-formed enamines were less explored until our communication.[2,11] We performed the search for suitable amine-based catalysts by evaluation of amine-acid and amine-acid-additive combinations in the reaction of enone **1a** and isatin **2a** to give hDA reaction product **3aa** in high yield with high diastereo- and enantioselectivities.[2] The catalyst system composed of amine **A**, acid **B**, thiourea **C** was identified as the best among those tested (Scheme 2). Selected results of the screening from our previous report[2,3] are shown in Table 1. The enantioselectivity of **3aa** was higher in the reaction using the three-component catalyst system composed of **A**, **B**, and **C** than in the reactions using only **A** and **B** or only **A** and **C** (entries 1, 2, and 5 versus entries 3 and 4). The reaction catalyzed by only amine **A** and acid **B** without thiourea **C** was slower than the reaction catalyzed by the combination of **A**, **B**, and **C** (entry 3). In addition, reaction in the presence of **B** and **C** without amine **A** did not afford **3aa**. Thus, the three components, amine **A**, acid **B**, and thiourea **C**, are needed to obtain the hDA reaction product in high conversion or yield with high diastereo- and enantioselectivity.[2,3] When the loadings of acid **B** and thiourea **C** were increased, the reaction with a reduced loading of amine **A** also afforded product **3aa** with high diastereo- and enantioselectivities (entry 6). Effects of loadings of the catalyst components are discussed in our report on the mechanism of the reaction.[3] The diastereomers of **3aa** were able to be obtained as single diastereomer by silica gel column purification, and the enantiomeric purity of the major enantiomer was able to be increased by crystallization.[2,3] The major stereoisomer of the product obtained by the reaction catalyzed by amine **A**, acid **B**, thiourea **C** was determined to be (2'*S*,6'*R*)-**3aa** by the X-ray crystal structural analysis of the *p*-toluenesulfonohydrazide derivative.[2]

Using the catalyst system composed of amine **A**, acid **B**, and thiourea **C**, various hDA products **3** were obtained under mild conditions (Charts 1 and 2).[2,3] Reactions of substituted isatins and functionalized α,β-unsaturated ketones (such as phthalimide-, siloxy-, and halide-bearing enones) also afforded the corresponding hDA reaction products.



Scheme 2. Catalyst system identified for the diastereo- and enantioselective hDA reaction.

Table 1. Catalyst Systems for the Synthesis of **3aa**.[a]

entry	Amine (equiv)	acid (equiv) + additive (equiv)	time (h)	<conversion> or yield (%)[b]	dr[c]	ee (%)[d]
1	**A** (0.2)	**B** (0.4) + **C** (0.2)	18	<100>	18:1	93
2[e]	**A** (0.1)	**B** (0.2) + **C** (0.1)	48	<59>	8.0:1	94
3	**A** (0.2)	**B** (0.4)	48	<77>	11:1	87
4[f]	**A** (0.2)	**C** (0.6)	48	<100>	1.0:1	62
5[g]	**A** (0.2)	**B** (0.4) + **C** (0.2)	18	67	18:1	93
6[h]	**A** (0.1)	**B** (0.8) + **C** (0.4)	48	93	15:1	94

[a] Reaction was performed using enone **1a** (0.5 mmol) and isatin **2a** (0.1 mmol) in the presence of amine (0.02 mmol) and acid (0.04 mmol) with or without additive **C** (0.02 mmol) in toluene (0.2 mL) at 24 °C except as indicated. [b] Yield was isolated yield; conversion was determined by ^{1}H NMR based on the ratio of **3aa** to **2a**. [c] Determined by ^{1}H NMR. [d] The major diastereomer of **3aa**; determined by HPLC. [e] Amine **A** (0.01 mmol), acid **B** (0.02 mmol), and thiourea **C** (0.01 mmol) were used. [f] Thiourea **C** (0.06 mmol) were used. [g] Reaction was performed using enone (1.0 mmol) and isatin (0.2 mmol) in the presence of amine (0.04 mmol), acid (0.08 mmol), and thiourea (0.04 mmol) in toluene (0.4 mL). [h] Reaction was performed using enone (0.5 mmol) and isatin (0.1 mmol) in the presence of amine (0.01 mmol), acid (0.08 mmol), and thiourea (0.04 mmol) in toluene (0.2 mL).

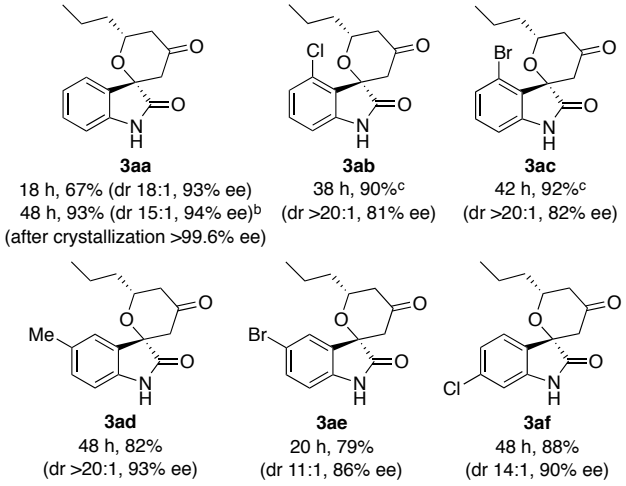


Chart 1. The hDA reaction products obtained from various isatins.[a]

[a] Reaction conditions: enone (1.0 mmol) and isatin (0.2 mmol) in the presence of amine **A** (0.04 mmol), acid **B** (0.08 mmol), and thiourea **C** (0.04 mmol) in toluene (0.4 mL) at 24 °C. [b] Reaction in the presence of **A** (0.01 mmol), **B** (0.08 mmol), and thiourea **C** (0.04 mmol); taken from Table 1, entry 6. [c] Reaction in the presence of **A** (0.02 mmol), **B** (0.04 mmol), and thiourea **C** (0.02 mmol).

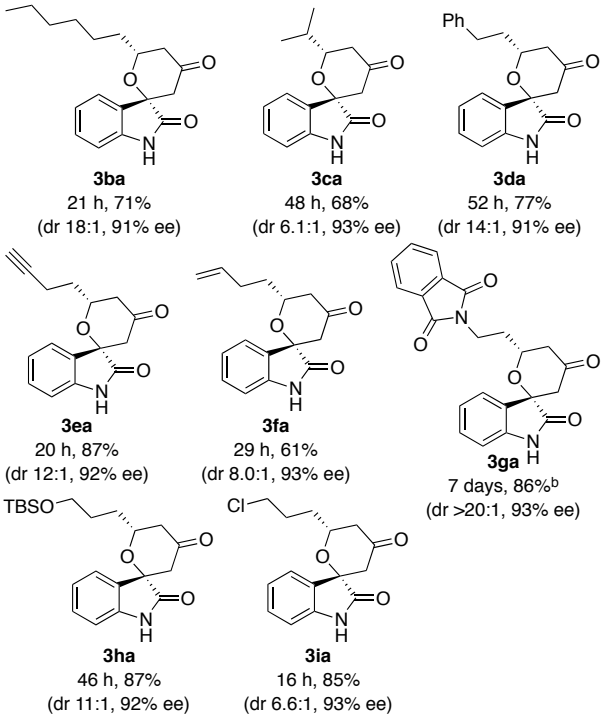
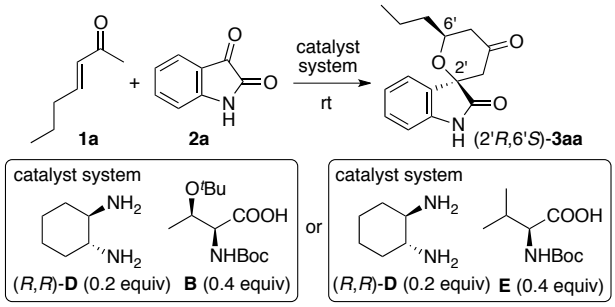


Chart 2. The hDA reaction products obtained from various enones.[a]

[a] Reaction conditions: enone (1.0 mmol) and isatin (0.2 mmol) in the presence of amine **A** (0.04 mmol), acid **B** (0.08 mmol), and thiourea **C** (0.04 mmol) in toluene (0.4 mL) at 24 °C. [b] Reaction in the presence of **A** (0.02 mmol), acid **B** (0.08 mmol), and thiourea **C** (0.04 mmol) in toluene (0.6 mL)-CH_2Cl_2 (0.4 mL).

The opposite enantiomer of the product obtained by the reaction catalyzed by **A**, **B**, and **C** was synthesized using amine (*R*,*R*)-**D** with acid **B** or **E** as the catalyst (Scheme 3, Table 2). The reaction using amine (*R*,*R*)-**D** and acid **E** as the catalyst gave (2'*R*,6'*S*)-**3aa** as the major stereoisomer, and the reaction using amine (*S*,*S*)-**D** and acid **E** as the catalyst gave (2'*S*,6'*R*)-**3aa** as the major stereoisomer. That is, the product stereochemistry relied on the configuration of amine **D**. Addition of thiourea **C** to the reaction catalyzed by amine **D** and acid **E** enhanced the reaction rate but did not improve the enantioselectivity.



Scheme 3. Catalyst systems for the synthesis of opposite enantiomer of the hDA product obtained using catalyst system composed of amine **A**, acid **B**, and thiourea **C**.

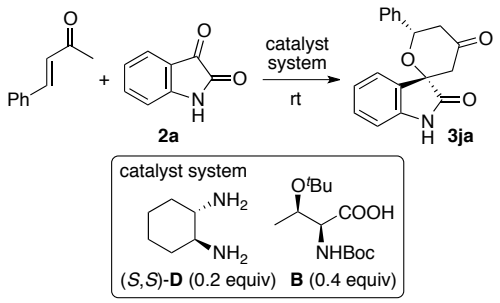
Table 2. Catalyst Systems for the Synthesis of **3aa**.[a]

entry	amine	acid + additive	time (h)	yield or <conversion> (%)[b]	dr[c]	ee (%)[d]
1	(*R*,*R*)-**D**	**B**	17	<100>	17:1	-79[e]
2	(*R*,*R*)-**D**	**E**	20	<100>	8.0:1	-85[e]
3[f]	(*R*,*R*)-**D**	**E** + **C**	5.5	<100>	8.7:1	-75[e]
4[g]	(*R*,*R*)-**D**	**E**	17	66	>20:1	-85[e]
5[g]	(*S*,*S*)-**D**	**E**	17	56	>20:1	90
6	(*S*,*S*)-**D**	**E**	7	83	14:1	86

[a] Reaction was performed using enone **1a** (0.5 mmol) and isatin **2a** (0.1 mmol) in the presence of amine (0.02 mmol) and acid (0.04 mmol) with or without additive **C** (0.02 mmol) in toluene (0.2 mL) at 24 °C except as indicated. [b] Yield was isolated yield; conversion was determined by ^{1}H NMR based on the ratio of **3aa** to **2a**. [c] Determined by ^{1}H NMR. [d] The major diastereomer of **3aa**; determined by HPLC. [e] Minus value indicates that the major isomer was (2'*R*,6'*S*)-**3aa**. [f] Thiourea **C** (0.2 mmol) was used. [g] Toluene (1.0 mL) was used.

Whereas various highly enantiomerically enriched hDA reaction products were synthesized using the catalyst system composed of amine **A**, acid **B**, and thiourea **C**, this catalyst system was not suitable for the reactions of 4-arylbut-3-ene-2-ones to afford hDA reaction products. The catalyst system composed of **A**, **B**, and **C** afforded the corresponding aldol as the major product compared to the hDA product. For the reaction of 4-phenylbut-3-ene-2-one, catalyst system composed of amine **D** and acid **B** gave hDA reaction product **3ja** (Scheme 4).

The diastereo- and enantioselectivities of the hDA reactions to give **3ja** depended on reaction time: The initially formed major diastereomer of **3ja** was gradually reduced, and this became the minor diastereomer after 6 days. The ee value of the initially formed major diastereomer was reduced with the dr changes as we reported in our mechanistic investigation paper.[3] After isolation of product **3ja**, no changes in dr and ee values were observed. With the use of the catalyst system composed of amine **D** and acid **B** for appropriate reaction time, enantiomerically enriched hDA reaction products from 4-arylbut-3-ene-2-ones were obtained as shown in Chart 3.



Scheme 4. Catalyst system for the hDA reaction of 4-arylbut-3-ene-2-ones.

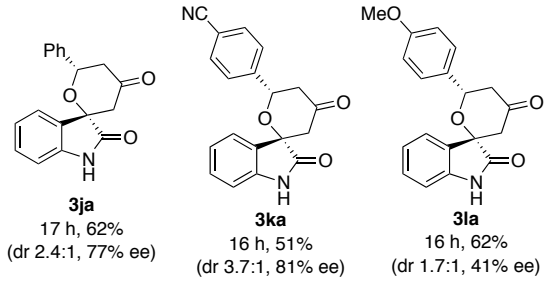
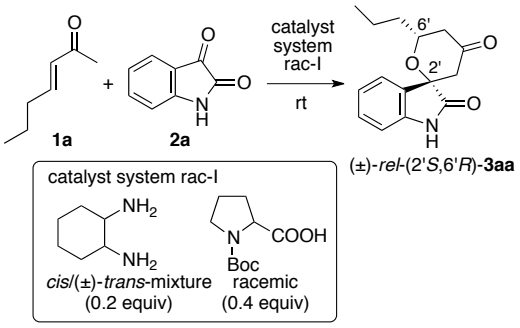


Chart 3. The hDA reaction products obtained from aryl enones.

Conditions for the synthesis of racemic products were also identified. For racemic synthesis, the *cis*/(±)-*trans*-mixture-1,2-diaminocyclohexane-(±)-*N*-Boc-proline system (catalyst system rac-I) was found to be efficient to afford the hDA reaction products in good yields with high diastereoselectivities (Scheme 5). Major diastereomers obtained by the methods shown in Scheme 5 were the same as the major diastereomers obtained using catalyst system composed of **A**, **B**, and **C** shown in Scheme 2. Note that when *cis*/(±)-*trans*-mixture-1,2-diaminocyclohexane-acetic acid system was used as catalyst, the dr value of the hDA reaction product was moderate (data not shown). Racemic hDA products with no or very low diastereoselectivities were also obtained using benzylamine and *N*-protected amino acid as catalyst.[3] For initial stages of biofunctional assays, racemic compounds may be used for identification of active molecules, avoiding doubled numbers of samples for testing each enantiomer of a compound. The compounds shown in Charts 1-3 were synthesized using catalyst system rac-I to provide the racemic versions. Products shown in Chart 4 were also obtained in reactions using the racemic catalyst system.



Scheme 5. Catalyst system for the synthesis of (±)-hDA products.

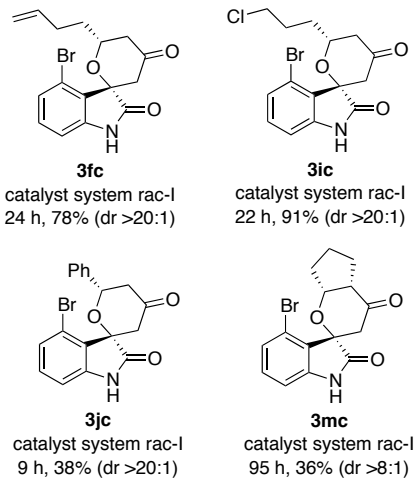


Chart 4. Racemic hDA reaction products synthesized using the racemic catalyst system.

Using these methods, hDA products were obtained as the major products under the appropriate conditions; however, small amount of aldol product was co-existed during the reaction.[2,3,12] Thus, aldols **4** and **4c** were also obtained (Chart 5). The aldol products should also be candidates of biofunctional molecules.

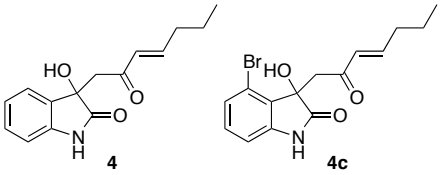


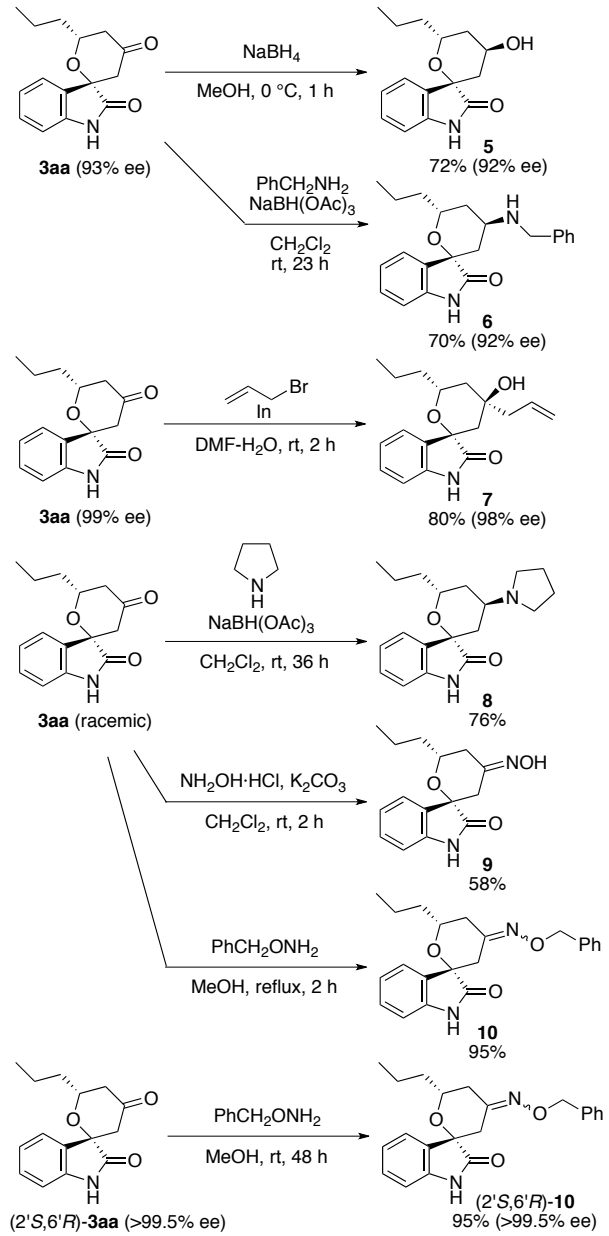
Chart 5. Aldol products obtained.

2. Transformations of the hetero Diels-Alder reaction products

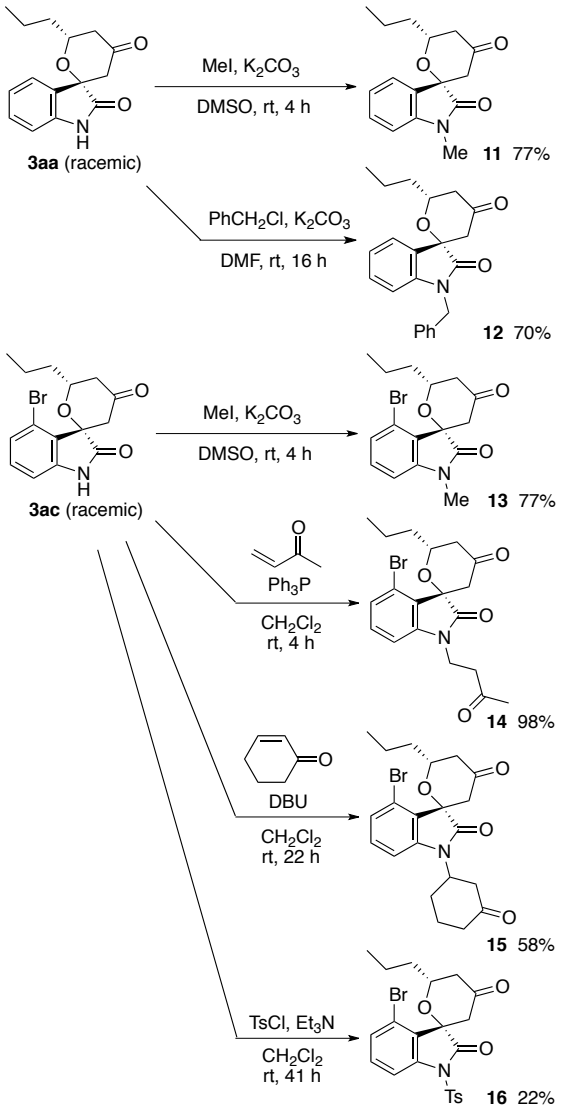
As described in our design, transformations of the obtained hDA products can further provide various functionalized molecules useful in searches for biofunctional molecules. To demonstrate the use of the hDA products for further transformations, several transformations at the ketone and the indole nitrogen were examined.

For transformation reactions at the ketone carbonyl group, for example, reduction, reductive ammination, allylation, and oxime formation were performed and products **5**-**10** were readily obtained (Scheme 6). When enantiomerically enriched hDA product **3aa** was used for the reactions, the transformed products retained the enantiopurity of the hDA product.

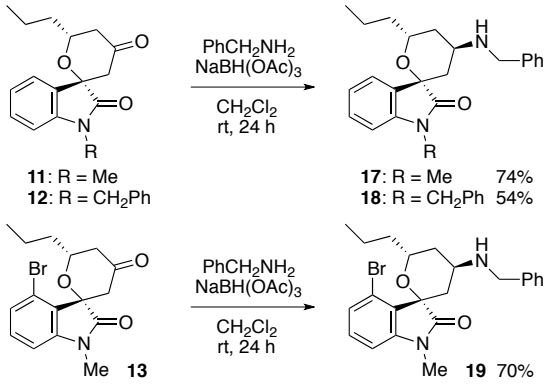
For reactions at the indole nitrogen, methylation, benzylation, alkylation through Michael additions, and tosylation were performed and products **11-16** were obtained (Scheme 7). The indole nitrogen-modified products were also used for reactions at the ketone carbonyl group to synthesize **17-19** (Scheme 8). The compound variations were concisely increased from the hDA products.



Scheme 6. Transformations of the hDA products at the ketone carbonyl group.



Scheme 7. Transformations of the hDA products at the indole nitrogen.



Scheme 8. Transformations of the indole nitrogen-modified hDA products.

3. Identification of biofunctional molecules from the hetero Diels-Alder reaction products and their derivatives

To demonstrate the usefulness of the hDA reaction methods and of the molecules obtained by the methods, nineteen (19) of the synthesized compounds were evaluated in an open innovation drug discovery system.[13] The 19 compounds were **3aa**, **3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ga**, **3ja**, **3fc**, **3jc**, **5**, **6**, **7**, **9**, **11**, **13**, **14**, **15**, and **16**. As described above, use of racemic versions of compounds minimizes the number of samples evaluated. Interesting compounds identified in assays of racemic compounds may be tested later by using each eanantiomer separately for further investigation. Thus, for these initial evaluations, we used racemic compounds.

In the screens, compound **6** was identified as an inhibitor (antagonist) of human ion channel Nav1.7; the IC_{50} was determined to be 1.0 μM. The human Nav1.7 has recently proposed as a target for pain reduction.[14] None of other 18 compounds tested inhibited the human Nav1.7 activity (<50% inhibition at compound concentration 3 μM). As this initial phase of synthesis and screening resulted in an inhibitor with activity at the 1 μM-level, further analyses of compounds accessed using our developed hDA reaction methods should lead to discovery of functional molecules. As the spirooxindole tetrahydropyranone core synthesized by our hDA reaction methods can easily have functionalized substituents that point in four directions in the three-dimensional space, our methods may be useful for further structure-activity relationship analyses and for the discovery of other biofunctional molecules.

Conclusions

We have developed the hDA reactions of enones with isatins catalyzed by amine-based catalyst systems and have expanded the scope of the hDA reactions. With the developed catalyst systems, various spirooxindole tetrahydropyranones were synthesized either in enantiomerically enriched forms or in racemic forms. Further, we have demonstrated that the hDA reaction products can be transformed at the ketone carbonyl group and the indole nitrogen. Using these reactions, various functionalized spirooxindole tetrahydropyran derivatives were concisely obtained. From the synthesized compounds, an inhibitor of ion channel Nav1.7 with the IC_{50} of 1.0 μM was identified. Our developed hDA reaction methods and further transformations of the hDA products will provide molecules useful for discoveries of biofunctional molecules. We are continuing the search of functional molecules from the pool of the compounds synthesized using our hDA reaction methods. The results will be reported in due course.

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Footnotes (First page)

[a] Chemistry and Chemical Bioengineeing Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan.
E-mail: ftanaka@oist.jp

† Electronic Supplementary Information (ESI) available: Synthesis and characterization of compounds.

Notes and references

For H.-L. Cui, present address: Chongqing University of Arts and Sciences, 319 Honghe Ave., Yongchuan, Chongqing 402160 (P. R. China).

1 T. E. Nielsen and S. L. Schreiber, *Angew. Chem., Int. Ed.* 2008, **47**, 48 and references cited therein.

2. H.-L. Cui, F. Tanaka, *Chem.–Eur. J.* 2013, **19**, 6213-6216.

3. H.-L. Cui, P. V. Chouthaiwale, F. Yin, F. Tanaka, *Asian J. Org. Chem.* in press, DOI: 10.1002/ajoc.201500412.

4. (a) G. S. Singh, Z. Y. Desta, *Chem. Rev.* 2012, **112**, 6104-6155; (b) N. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* 2012, **10**, 5165-5181; (c) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas, *ACS Catal.* 2014, **4**, 743-762 and references cited therein; (d) A. K. Franz, P. D. Dreyfuss, S. L. Schreiber, *J. Am. Chem. Soc.* 2007, **129**, 1020-1021.

5. (a) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem, Int. Ed.* 2009, **48**, 7200-7203; (b) Y. B. Lan, H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao, X.-W. Wang, *Org. Lett.* 2011, **13**, 4866-4869; (c) G. Li, T. Liang, L. Wojtas, J. C. Antilla, *Angew. Chem., Int. Ed*. 2013, **52**, 4628-4632; (d) L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu, L.-X. Wang, *Chem. Commun*. 2010, **46**, 8064-8066; (e) Q. Wei, L.-Z. Gong, *Org. Lett.* 2010, **12**, 1008-1011; (f) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* 2012, **41**, 7247-7290.

6. Synthesis of spirooxindole tetrahydro-4-pyranones: (a) J. Wang, E. A. Crane, K. A. Scheidt, *Org. Lett.* 2011, **13**, 3086-3089; (b) L. Liu, P. Daka, R. Sarkisian, Y. Deng, K. Wheeler, H. Wang, *Synthesis* 2014, **46***,* 1339-1347.

7. Synthesis of spirooxindole dihydro-4-pyranones: (a) T. Liang, G. Li, L. Wojtas, J. C. Antilla, *Chem. Commun.* 2014, **50***,* 14187-14190; (b) Q. Wang, Z. Lian, Q. Xu, M. Shi, *Adv. Synth. Catal.* 2013, **355**, 3344-3350. Synthesis of spirooxindoles with lactones, dihydropyranols, and other oxgen-containing 6-membered rings: (c) T.-P. Gao, J.-B. Lin, X.-Q. Hu, P.-F. Xu, *Chem. Commun.* 2014, **50***,* 8934-8936; (d) J. Zheng, L. Lin, Y. Kuang, J. Zhao, X. Liu, X. Feng, *Chem. Commun.* 2014, **50***,* 994-996; (e) C. Cassani, P. Melchiorre, *Org. Lett.* 2012, **14**, 5590-5593.

8. Amine-based organocatalytic reactions to generate tetrahydro-4-pyranones: (a) L.-Q. Lu, X.-N. Xing, X.-F. Wang, Z.-H. Ming, H.-M. Wang, W.-J. Xiao, *Tetrahedron Lett.* 2008, **49**, 1631-1635; (b) Y.-J. Lin, L.-N. Du, T.-R. Kang, Q.-Z. Liu, Z.-Q. Chen, L. He, *Chem.–Eur. J.* 2015, **21**, 11773-11778.

9. Amine-based organocatalytic Diels-Alder reactions to generate cyclohexanones and cyclohexens via the enamine formation in situ: (a) R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas, *Tetrahedron Lett.* 2002, **43**, 3817-3820; (b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem., Int. Ed.* 2003, **42**, 4233-4237; (c) L. Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* 2009, **48**, 7196-7199; (d) X. Feng, Z. Zhou, R. Zhou, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *J. Am. Chem. Soc.* 2012, **134**, 19942-19947; (e) F. Eudier, P. Righi, A. Mazzanti, A. Ciogli, G. Bencivenni, *Org. Lett.* 2015, **17**, 1728-1731. Diels-Alder reactions of trienamines: (f) X.-F. Xiong, Q. Zhou, J. Gu, L. Dong, T.-Y. Liu, Y.-C. Chen, *Angew. Chem., Int. Ed.* 2012, **51**, 4401-4404; (g) J. Stiller, D. Kowalczyk, H. Jiang, K. A. Jorgensen, L.

Albrecht, *Chem.–Eur. J.* 2014, **20**, 13108-13112. Enamine-based aza-Diels-Alder reactions of enones: (h) M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa, E. N. Jacobsen, *J. Am. Chem. Soc.* 2013, **135**, 1891-1894 and references cited therein; (i) Y. Liu, T. R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L.Yang, L. He, *Org. Lett.* 2013, **15**, 6090-6093; (j) H. Hu, C. Meng, Y. Dong, X. Li, J. Ye, *ACS Catal.* 2015, **5**, 3700-3703. Amine-catalyzed Diels-Alder reactions of enones, in which enamines of enones were not involved to initiate the reactions: (k) N. Halland, P. S. Aburel, K. A. Jorgensen, *Angew. Chem., Int. Ed.* 2004, **43**, 1272-1277; (l) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J. G. Deng, *Angew. Chem., Int. Ed.* 2007, **46**, 389-392. Enamine-based formal hetero-Diels-Alder reactions of enones with nitroso compounds: (m) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* 2004, **126**, 5962-5963. Enamine-based cycloadditions and cyclizations: (n) A. Moyano, R. Rios, *Chem. Rev.* 2011, **111**, 4703-4832.

10 Enamine activation of aldehydes in Diels-Alder and related reactions: (a) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* 2012, **45**, 1491-1500 and cited therein; (b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* 2010, **2**, 167-178; (c) Q. Wang, Z. Lian, Q. Xu, M. Shi, *Adv. Synth. Catal.* 2013, **355**, 3344-3350; (d) C. Cassani, P. Melchiorre, *Org. Lett.* 2012, **14**, 5590-5593.

11 Diels-Alder and related reactions of silyl enol ether-derived dienes, siloxybutadiene derivatives, and preformed enamines as dienes: (a) A. G. Dossetter, T. F. Jamison, E. N. Jacobsen, *Angew. Chem., Int. Ed.* 1999*,* **38***,* 2398-2400; (b) Y. Yamashita, S. Saito, H. Ishitani, S. Kobayashi, *J. Am. Chem. Soc.* 2003, **125**, 3793-3798; (c) M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro, S. Hashimoto, *Angew. Chem., Int. Ed.* 2004, **43**, 2665-2668; (d) A. K. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc.* 2005, **127**, 1336-1337; (e) S. Rajaram, M. S. Sigman, *Org. Lett.* 2005, **7**, 5473-5475; (f) N. Momiyama, H. Tabuse, M. Terada, *J. Am. Chem. Soc.* 2009, **131**, 12882-12883; (g) J. Guin, C. Rabalakos, B. List, *Angew. Chem., Int. Ed.* 2012, **51**, 8859-8863.

12 Previously reported reactions of enones with aldehydes or ketones including isatins have often afforded only aldol products: (a) B. M. Trost, S. Shin, J. A. Sclafani, *J. Am. Chem. Soc.* 2005, **127**, 8602-8603; (b) Q. Guo, M. Bhanushali, C.-G. Zhao, *Angew. Chem., Int. Ed.* 2010, **49**, 9460-9464; (c) G. Pousse, F. Le Cavelier, L. Humphreys, J. Rouden, J. Blanchet, *Org. Lett.* 2010, **12**, 3582-3585; (d) G.-G. Liu, H. Zhao, Y.-B. Lan, B. Wu, X.-F. Huang, J. Chen, J.-C. Tao, X.-W. Wang, *Tetrahedron* 2012, **68**, 3843-3850; (e) T. Yan, X. Wang, H. Sun, J. Liu, Y. Xie, *Molecules* 2013, **18**, 14505-14518; (f) C. Baker-Glenn, N. Hodnett, M. Reiter, S. Ropp, R. Ancliff, V. Gouverneur, *J. Am. Chem. Soc.* 2005, **127**, 1481-1486; (g) S. Abbaraju, J. C.-G. Zhao, *Adv. Synth. Catal.* 2014, **356**, 237-241.

13 URL: https://openinnovation.lilly.com/dd/what-we-offer/screening.html

14 (a) H. Bregman, L. Berry, J. L. Buchanan, A. Chen, B. Du, E. Feric, M. Hierl, L. Huang, D. Immke, B. Janosky, D. Johnson, X. Li, J. Ligutti, D. Liu, A. Malmberg, D. Matson, J. McDermott, P. Miu, H. N. Nguyen, V. F. Patel, D. Waldon, B. Wilenkin, X. M. Zheng, A. Zou, S. I. McDonough, E. F. DiMauro, *J. Med. Chem.* 2011, **54**, 4427-4445; (b) B. S. Williams, J. P. Felix, B. T. Priest, R. M. Brochu, K. Dai, S. B. Hoyt, C. London, Y. S. Tang, J. L. Duffy, W. H. Parsons, G. J. Kaczorowski, M. L. Garcia, *Biochemistry* 2007, **46**, 14693-14703; (c) S. Chowdhury, M. Chafeev, S. Liu, J. Sun, V. Raina, R. Chui, W. Young, R. Kwan, J. Fu, J. A. Cadieux, *Bioorg. Med. Chem. Lett.* 2011, **21**, 3676-3681; (d) C. London, S. B. Hoyt, W. H. Parsons, B. S. Williams, V. A. Warren, R. Tschirret-Guth, M. M. Smith, B. T. Priest, E. McGowan, W. J. Martin, K. A. Lyons, X. Li, B. V. Karanam, N. Jochowitz, M. L.

Garcia, J. P. Felix, B. Dean, C. Abbadie, G. J. Kaczorowski, J. L. Duffy, *Bioorg. Med. Chem. Lett.* 2008, **18**, 1696-1701.