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Asymmetric HDA Reaction

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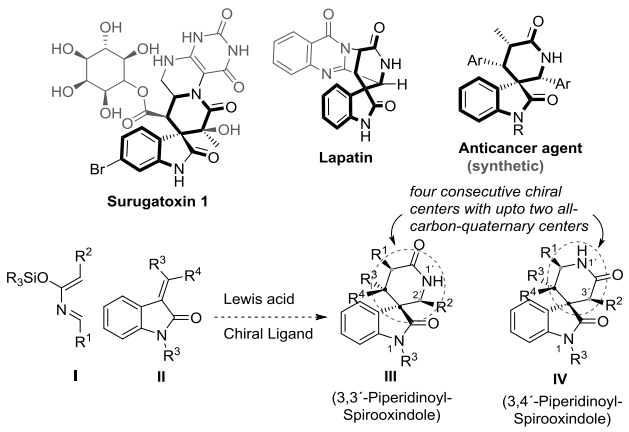
A Tunable and Enantioselective Hetero-Diels-Alder Reaction Provides Access to Distinct Piperidinoyl Spirooxindoles*

*Samydurai Jayakumar, Kathrin Louven, Carsten Strohmann and Kamal Kumar**

Dedicated to Prof. Dr. Herbert Waldmann on the occasion of his 60th birthday

***Abstract**: The active complexes of chiral N,N-oxide ligand with dysprosium and magnesium salts catalyze the hetero-Diels-Alder reaction between 2-aza-3-silyloxy-butadienes and alkylidene oxindoles to selectively form 3,3´- and 3,4´-piperidinoyl spirooxindoles respectively in very high yields and with excellent enantioselectivities. The exo-selective asymmetric cycloaddition successfully regaled the construction of sp^3 rich and highly substituted natural product based spirooxindoles supporting many chiral centers including consecutive all-carbon-quaternary centers.*

In the quest for gaining asymmetric synthetic access to heterocyclic scaffolds existing in natural product structures as well as synthetic bioactive molecules, the hetero-Diels-Alder (HDA) reaction is undoubtedly amongst the most efficient tools in a chemist´s toolbox.[1] Ghosez and coworkers introduced the HDA reaction of 2-aza-3-silyloxy-1,3-butadienes (2-ASBs, **I**, Scheme 1) with carbonyl compounds as well as electron-poor olefins in 90´s.[2] Strangely, since its inception and in more than 30 years, only one asymmetric HDA reaction of 2-ASBs with olefinic dienophiles was reported in 1999 by the Ghosez lab using conjugated imides.[3] Our interest in developing asymmetric annulation and cycloaddition reactions[4] affording natural product based scaffolds that are rich in stereogenic centers inspired us to explore this intriguing and potentially useful chemical transformation.[5] We envisioned that a chiral metal complex as Lewis acid could catalyze the HDA reaction of 2-ASBs with isatin-derived olefins (**II**) in asymmetric fashion and that might be tuned to selectively afford enantiomerically enriched 3,3´- or 3,4´-piperidinoyl-spirooxindoles **III** and **IV** respectively. Notably, the piperidinoyl-spirooxindole cores represent vital elements of biologically intriguing natural products[6] that are often decorated with up to four consecutive chiral centers (Scheme 1).[7]



Scheme 1. Biologically active piperidinoyl spirooxindoles and the strategy to make them *via* HDA reaction.

Initially, the racemic HDA reaction of trimethylsilyl (TMS)-azadiene **1a** with cyano substituted alkylidene *N*-Boc-oxindole **3a** was performed by heating the mixture in toluene at 110 °C for 4 h. The racemic cycloadduct **4a** was obtained in quantitative yield and with >10:1 diastereomeric ratio. Towards asymmetric cycloaddition reaction between **1a** and **3a**, unfortunately the reported catalytic system of copper triflate complexed with C_2-symmetric bis-oxazoline ligand **A**[3] did not provide any enantioselectivity, although the adduct **4a** was obtained in 64% yield. Therefore, a number of transition metal salts of silver, copper and magnesium in combination with various chiral ligands were attempted in the reaction of **1a** with olefin **3a**. Although the reactions yielded the desired adduct in moderate to high yields, no enantioselectivity was observed (see Supporting information, Table S1).

We suspected that the nucleophilic azadiene **1a** might have poisoned the Lewis acid metal complex and thereby facilitated the non-catalytic racemic synthesis of **4a**. We reasoned that a bulkier silyl group might sterically prevent such an interaction of imine nitrogen with metal complex, favours dienophile-catalyst interaction and facilitates the stereoselective cycloaddition reaction (Supporting information, Scheme S1). The reaction of **2a** supporting a bulky TBS group with **3a** in the presence of copper triflate and bis-oxazoline (**A**) as catalytic complex yielded the desired adduct **4a** in high yield (84%) and good diastereoselectivity. However the enantioselectivity still remained elusive in this reaction (Table 1, entry 1). Nevertheless, further reaction condition optimization was performed using more stable diene **2a** with olefin **3a** (Table 1).

Different chiral Lewis acid complexes of indium, zinc, magnesium, rhodium and titanium did support the HDA reaction[8] and provided very high diastereoselectivities (Table 1, entries 2-6), yet only racemic adduct **4a** was obtained. The first ray of hope in

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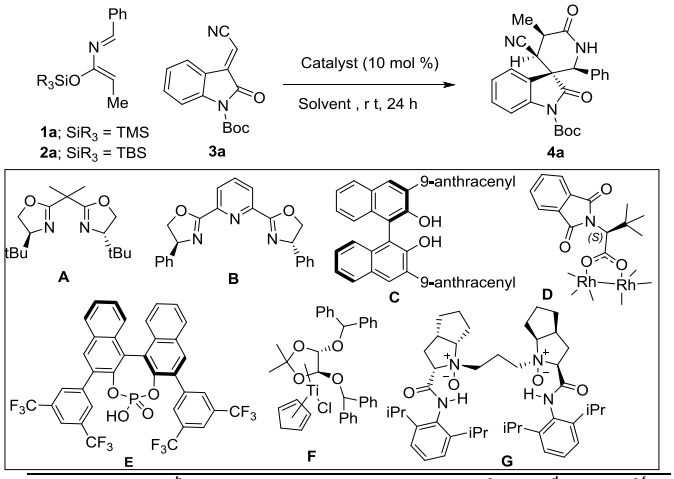
this optimization appeared when magnesium perchlorate in complex with *N*,*N*-oxide ligand **G** afforded **4a** in excellent yield and with 78% ee (Table 1, entry 7). Feng group had successfully used this class of ligands in a number of diverse asymmetric cycloaddition and cyclization reactions,[9] including HDA reaction of Brassard-type and Danishefsky´s dienes.[10] Nickel triflate with **G** catalyzed the reaction to give **4a** in high yield and slightly improved ee (Table 1, entry 8). However, copper triflate with **G** could hardly provide any enantioselectivity in the reaction (Table 1, entry 9). Zinc triflate did not make improvement over magenisum perchlorate (Table 1, entry 10).

Table 1. Optimization of enantioselective HDA reaction of 2-ASBs.[a]

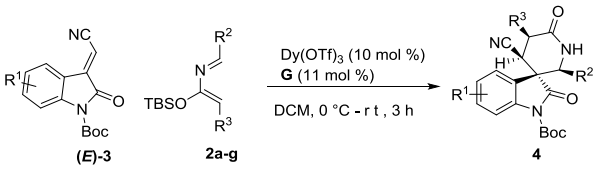


No.	Catalyst[b]	Ligand	Solvent	Yield (%)[c]	dr[d] 4a	ee[e,f] (%)
1	$Cu(OTf)_2$	**A**	DCM	84	16:1	0
2	InI_3	**B**	DCM	96	17:1	0
3	$ZnEt_2$	**C**	Et_2O	98	15:1	0
4	----	**D** -----	DCM	98	>20:1	0
5	$Mg(O^tBu)_2$	**E**	DCM	93	>20:1	0
6	-----	**F** -----	DCM	96	>20:1	0
7	$Mg(ClO_4)_2$	**G**	DCM	99	>20:1	(+)78
8	$Ni(OTf)_2$	**G**	DCM	94	>20:1	(+)81
9	$Cu(OTf)_2$	**G**	DCM	99	>20:1	(+)06
10	$Zn(OTf)_2$	**G**	DCM	99	>20:1	(+)76
11	$Yb(OTf)_3$	**G**	DCM	87	>20:1	(-)48
12	**$Dy(OTf)_3$**	**G**	**DCM**	**94**	**>20:1**	**(-)98**
13	$Dy(OTf)_3$	**G**	DCM	52	9.5:1	(-)34[g]
14	$LaOTf)_3$	**G**	DCM	98	>20:1	(-)90
15	$Nd(OTf)_3$	**G**	DCM	99	>20:1	(-)78
16	$Eu(OTf)_3$	**G**	DCM	99	>20:1	(-)74

[a] At the scale of 0.05 mmol of **3a** and 0.075 mmol of **2a** at 0.033 M conc.; [b] based on **3a**; [c] isolated yields; [d] determined by ^{1}H NMR; [e] determined by chiral HPLC for major diastereomer; [f] (+) and (-) refers to the clock- and anticlockwise direction respectively of the measured specific optical rotation of the adduct; [g]0.075 mmol of **1a** was used instead of **2a**.

When resorted to chiral lanthanide metal complexes as Lewis acid catalysts for the HDA reaction, ytterbium triflate with **G** led to a moderate enantioselectivity (Table 1, entry 11). To our delight, dysprosium triflate in combination with ligand **G** steered the HDA reaction efficiently and providing *exo*-cycloadduct **4a** with excellent enantiomeric excess of 98% (entry 12, Table 1). Under the same reaction condition, TMS azadiene **1a** failed to provide acceptable yield and enantioselectivity, plausibly owing to its nucleophilic character (entry 13, Table 1, see Supporting Scheme S1). Some other lanthanides were also tested for the HDA reaction of **2a** with **3a**, however none of them appeared better than dysprosium (Table 1, entries 14-16). Further reaction screening using 10 mol % of $Dy(OTf)_3$ and a series of chiral *N*,*N*-oxide ligands in different solvents revealed that ligand **G** (11 mol %) in dichloromethane offered the best reaction conditions for an asymmetric HDA reaction between **2a** and **3a** (see supporting Table S2-3). Notably, trivalent and divalent metal complexes with ligand **G** delivered opposite enantiomers of adduct **4a** (*cf.* entries 7-10 *vs* 12-16, Table 1) and thus offer construction of both enantiomers of piperidinoyl-spirooxindole with the help of just one chiral ligand.

Table 2. Scope of the asymmetric HDA reaction of 2-ASBs to yield 3,3´-piperidinoyl-spirooxindoles.[a]



No.	R^1	R^2	R^3	Yield 4 (%)[b]	dr[c]	ee[d,e] (%)
1	H	Ph	Me	**4a** (94)	>20:1	98
2	5-F	Ph	Me	**4b** (93)	14:1	96
3	5-Cl	Ph	Me	**4c** (85)	>20:1	96
4	5-Br	Ph	Me	**4d** (86)	>20:1	96
5	5-I	Ph	Me	**4e** (93)	>20:1	94
6	7-F	Ph	Me	**4f** (93)	>20:1	99
7	7-Br	Ph	Me	**4g** (94)	>20:1	96
8	5-NO_2	Ph	Me	**4h** (97)	6.2:1	40
9	5-Me	Ph	Me	**4i** (85)	>20:1	94
10	5-OMe	Ph	Me	**4j** (86)	>20:1	97
11	5-OCF_3	Ph	Me	**4k** (85)	>20:1	94
12	5,7-Me_2	Ph	Me	**4l** (87)	>20:1	81
13	H	Ph	^{n}Pr	**4m** (99)	>20:1	96
14	H	Ph	^{t}Bu	**4n** (98)	>20:1	98
15	H	4-F-C_6H_4	Me	**4o** (93)	>20:1	66
16	H	2-Furan	Me	**4p** (97)	>20:1	38

[a] At the scale of 0.05 mmol of **3a** at 0.033 M concentration; [b] isolated yields; [c] determined by ^{1}H NMR; [d] determined by chiral HPLC; [e] for major diastereomer.

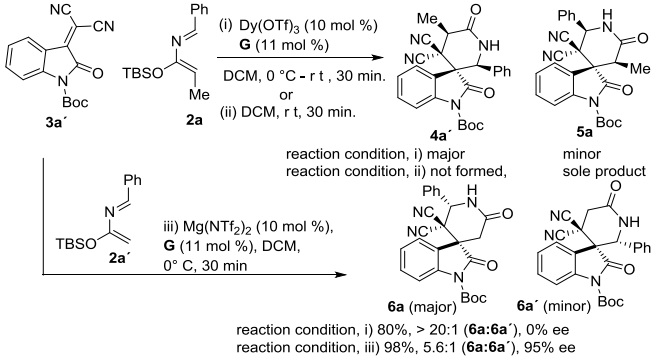
Further scope of the reaction to form substituted 3,3´-piperidinoyl-spirooxindoles was investigated using substituted isatine-derived *E*-olefins **3** as well as differently substituted 2-ASBs **2** (Table 2). The absolute configuration of adducts **4a-p** was established on the basis of x-ray diffraction analysis of **4k** (see Supporting information).

2-ASB **2a** reacted smoothly with a number of alkylidene oxindoles decorated with electron withdrawing groups and afforded spirooxindole **4b-g** in high yields and with excellent ee´s (Table 2, entries 2-7). A drastic reduction in enantio- and diastereoselectivity was observed in **4h** and could be attributed to the competitive coordination of 5-NO_2 group with catalyst (Table 2, entry 8). Electron-rich alkylidene oxindoles were also well tolerated under optimized reaction conditions providing methyl, methoxy, trifluoromethoxy as well as 5,7-di-methyl substitution on to the core scaffold and without compromising efficiency or enantioselectivity (**4i-l**, Table 2, entries 9-12). We also tested some variations on the azadiene itself. Interestingly, different alkyl groups on the diene including bulky *tert*-butyl group were well tolerated affording spirooxindoles **4m-n** in excellent yields and with excellent enantio- and diastereoselectivities (Table 2, entries 13-14). However, when 1-aryl-4-alkyl azadienes were used, moderate to low enantioselectivity was observed, although the cycloadducts **4o-p** were obtained in very high yields (Table 2, entries 15-16). Overall, dysprosium triflate in combination with *N*,*N*-oxide ligand **G** catalyzed a highly regio- and enantioselective HDA reaction between 2-ASB´s **2** and isatin-derived olefins **3** to provide 3,3´-piperdinoyl- spirooxindoles as *exo*-adducts in excellent yields. No trace of *endo*-adduct was observed.[11]

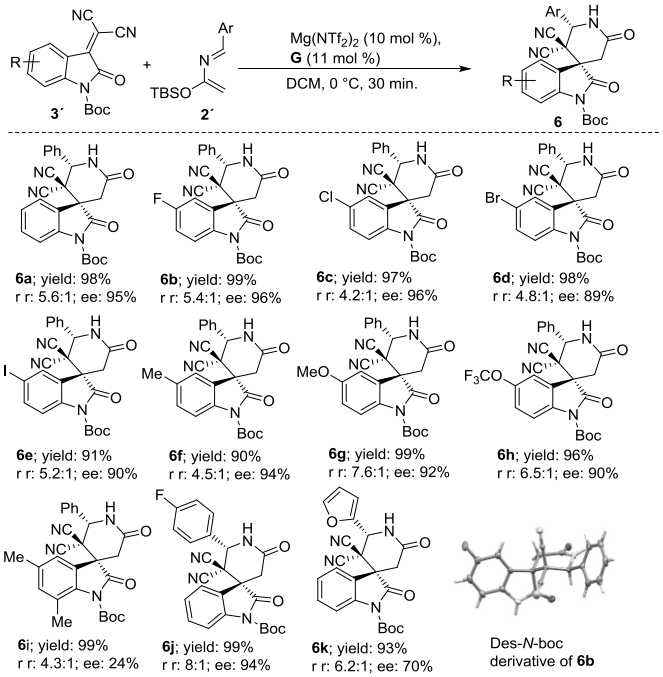
Many natural products, for instance, Surugatoxin also embodies 3,4´-piperidinoyl-spirooxindole scaffold.[7b, 7c] We wondered if the

10.1002/anie.201708355

HDA reaction can be tuned to selectively form this core framework. As we did not find a trace of this regioisomer formed in above HDA reaction, we hypothesized that modulating the direction of electrophilicity in the olefin might result into selective formation of 3,4´-piperidinoyl-spirooxindole. To this end, dicyano alkylidene oxindole **3a´** was explored with 2-ASB **2a** under the above optimized reaction conditions. To our surprise, this very fast asymmetric HDA reaction delivered the desired adduct **5a** as minor product and 3,3´-piperidinoyl-spirooxindole **4a´** was obtained as the major product. Unfortunately, all our attempts to resolve **4a´** using different chiral stationary phases failed and the enantiomeric excess could not be ascertained. Very intriguingly, the non-catalyzed reaction of **3a´** and **2a** yielded the desired racemic adduct **5a** as the sole product (Scheme 2 and Supporting Table S4). Resorting to azadiene **2a´** lacking a substitution on the silyl enol, the reaction afforded the desired spirooxindole **6a** as the major product (dr > 20:1) along with minor regioisomer **6a´** (Scheme 2). However, no enantioselectivity was observed in this reaction.



Scheme 2. Reaction of dicyano alkylidene oxindole **3a´** with 2-ASB **2a**.

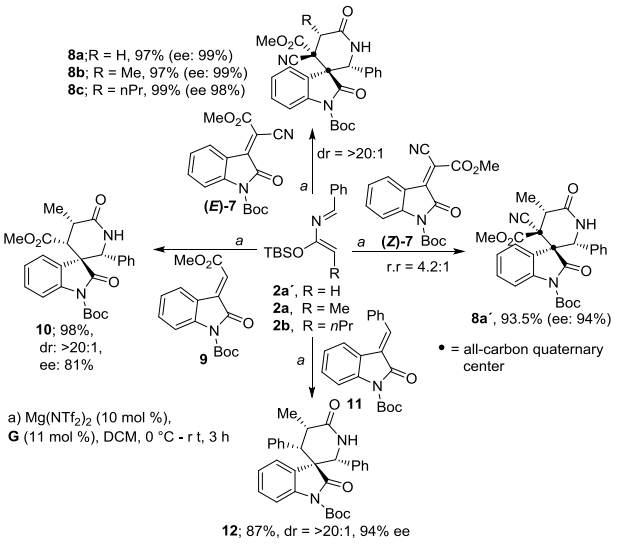


Scheme 3. Scope of enantioselective HDA reaction of monosusbtituted 2-ASBs to form 3,4´-piperidinoyl-spirooxindoles.

A further exploration of tri- and divalent metal complexes with ligand **G** unravelled magnesium(II) bis(trifluoromethanesulfonyl)-imide as the best Lewis acid to catalyze asymmetric HDA reaction between oxindole **3a´**and 2-ASB **2a** to afford the desired adduct **6a** in excellent yield and enantiomeric excess (see Supporting Table S5-6).

The scope of newly optimized reaction condition to form substituted 3,4´-piperidinoyl-spirooxindoles was evaluated by employing differently substituted dicyano-alkylidene oxindoles **3´** in reaction with 2-ASB **2´** (Scheme 3). Electron-withdrawing as well as donating substitutions on the oxindole aryl ring were nicely tolerated to afford corresponding spirooxindoles **6a-h** in excellent yields and in most cases with excellent enantioselectivities (Scheme 3). In the reaction of 5,7-dimethyl alkylidene oxindole, a detrimental reduction in enantioselectivity to form adduct **6i** was observed, probably owing to the steric reasons. Varying aryl substitutions on the azadiene part successfully afforded the corresponding adducts **6j** and **6k** with excellent and moderate enantioselectivity respectively (Scheme 3). Absolute stereochemistry of the adducts was established on the basis of x-ray crystal structure of a derivative of adduct **6b** (Scheme 3).

The optimized HDA reactions of 2-ASBs and alkylidene oxindoles address one of the most daunting challenges in asymmetric organic syntheses, *i.e.* formation of a number of consecutive stereogenic centers.[12] In this regard, we targeted highly complex piperidinoyl spirooxindoles bearing four consecutive stereogenic centers including two vicinal all-carbon-quaternary centers.[13] To this end, (*E*)- and (*Z*)-alkylidene oxindoles **7** supporting an ester and cyano function on olefin were employed in the HDA reaction with 2-ASBs. To our delight, the reaction of ***E*-7** olefin with mono-substituted 2-ASB **2a´** afforded the 3,3´-piperidinoyl-spirooxindole **8a** as the major product in excellent yield and with excellent enantioselectivity (Scheme 4). Formation of **8a** as the major product further supports our earlier observation that steric factors favored the formation of 3,3´-piperidinoyl-spirooxindole scaffold over 3,4´-piperidinoyl spirooxindoles. The *E*-**7** olefin could also smoothly react with 1,4-disubstituted 2-ASB **2a-b**, giving spirooxindoles **8b-c** supporting four consecutive chiral centers including two *consecutive all-carbon-quaternary* centers, in good yields and with excellent enantioselectivities (Scheme 4). Using ***Z*-7** as dienophile with **2a** afforded the expected adduct **8a´** as the major adduct with moderate regioselectivity. However, the catalytic system developed could maintain the excellent enantioselectivity in this case too (Scheme 4).



Scheme 4. Enantioselective HDA reaction of diverse oxindole dienophiles with 2-ASBs.

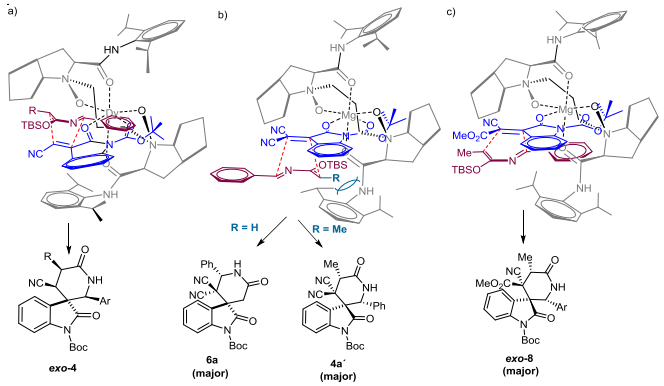
Further utility of asymmetric HDA reaction to deliver 3,3´-piepridinoyl spirooxindole scaffold decorated with important functional groups was demonstrated with the reactions of differently substituted alkylidene oxindoles. Thus, a reaction of oxindole *E*-**9** supporting an ester function on olefin with **2a** afforded the 3,3´-

10.1002/anie.201708355

spirooxindole **10** in excellent yield and with 81% ee (Scheme 4). Importantly, the ester function offers a synthetic handle that can be easily manipulated in compound collection synthesis.

Having biaryl groups in *syn*-configuration at 2´- and 4´-position on the 3,3´-piperidinoyl spirooxindole bequeaths anticancer activity to the molecules (Scheme 1).[7e] No enantioselective synthesis to this class of scaffold is yet known. Using magnesium salt with ligand **G**, the reaction of oxindole *E*-**11** bearing a phenyl substituted olefin and 2-ASB **2a**, afforded diphenyl substituted 3,3´-piperidinoyl spirooxindole **12** in very high yield and with excellent enantioselectivity and thus demonstrated the broader synthetic utility of the asymmetric HDA reaction (Scheme 4).

Mechanistically, ligand **G** acts as a tetradentate ligand to trivalent Dy(III) and along with alkylidene oxindole forms a distorted octahedral complex. *N*,*N*-oxides as well as the amide carbonyls of **G** stabilize the highly congested *exo*-transition state that strictly permits 2-ASB to approach only the *si*-face of cyano-olefin and form the *exo*-adduct **4** exclusively (Scheme 5a). However, the transition state of a relatively puckered divalent magnesium complex with ligand **G** and dicyano-alkylidene oxindole **3´** gets the *si*-face of olefin completely blocked and therefore azadiene approaches it from the *re*-face.[14] In this situation, 2-ASBs lacking 4-alkyl group (R = H) successfully form the 3,4´-piepidinoyl spirooxindole **6a**. However, 1,4-disubstituted 2-ASBs (e.g. R = Me) face steric hindrance from aryl groups of amide functions in ligand **G** and thus prefer to form 3,3´-piperidinoyl-spirooxindole **4a´** and *exo*-**8** (in case of disubstituted olefin (*E*)-**7**) *via* a flipped azadiene approach where we assume that the π-π interaction of aryl groups of diene and dienophile stabilize the complex (Scheme 5b-c).



Scheme 5. a) A transition state for *exo*-selective HDA reaction of mono-cyano alkylidene oxindoles **3** with 2-ASBs; b) a transition state for enantioselective HDA reaction of 2-ASBs (**2´**) with dicyano- (**3´**) and c) cyano, ester substituted alkylidene oxindoles (**7**).

In summary, we have developed highly enantioselective and easily tunable hetero-Diels-Alder reactions of 2-aza-silyloxy-1,3-butadienes with alkylidene oxindoles. In this rarely explored class of cycloaddition reactions, chiral *N*,*N*-dioxide ligand **G** in complex with dysprosium or magnesium metal salts regaled a facile and selective construction of 3,3´- and 3,4´-piperidinoyl-spirooxindoles respectively that represent scaffolds of biologically intriguing synthetic and natural small molecules. The disclosed asymmetric cycloaddition reaction can create molecular scaffolds beholding a number of consecutive chiral centers including all-carbon-quaternary centers in a very efficient manner and therefore can offer various applications in asymmetric organic synthesis of complex small molecules.

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[1] a) V. Eschenbrenner-Lux, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 11146-11157; b) G. B. Rowland, E. B. Rowland, Q. Zhang, J. C. Antilla, *Curr. Org. Chem.* **2006**, *10*, 981-1005; c) B. S. Bodnar, M. J. Miller, *Angew. Chem. Int. Ed.* **2011**, *50*, 5629-5646.

[2] a) A. Pouilhes, Y. Langlois, P. Nshimyumukiza, K. Mbiya, L. Ghosez, *B. Soc. Chim. Fr.* **1993**, *130*, 304-309; b) R. Beaudegnies, L. Ghosez, *Tetrahedron Asymm.* **1994**, *5*, 557-560; c) L. Ghosez, P. Bayard, P. Nshimyumukiza, V. Gouverneur, F. Sainte, R. Beaudegnies, H. Rivera, A. M. Frisquehesbain, C. Wynants, *Tetrahedron* **1995**, *51*, 11021-11042; d) F. Sainte, B. Serckxponcin, A. M. Hesbainfrisque, L. Ghosez, *J. Am. Chem. Soc.* **1982**, *104*, 1428-1430; e) J. M. Adam, L. Ghosez, K. N. Houk, *Angew. Chem. Int. Ed.* **1999**, *38*, 2728-2730; f) D. Ntirampebura, L. Ghosez, *Tetrahedron Lett.* **1999**, *40*, 7079-7082.

[3] E. Jnoff, L. Ghosez, *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618.

[4] a) B. Baskar, K. Wittstein, M. G. Sankar, V. Khedkar, M. Schurmann, K. Kumar, *Org. Lett.* **2012**, *14*, 5924-5927; b) A. Danda, N. Kesava-Reddy, C. Golz, C. Strohmann, K. Kumar, *Org. Lett.* **2016**, *18*, 2632-2635; c) V. Eschenbrenner-Lux, P. Kuchler, S. Ziegler, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 2134-2137.

[5] a) W. Zhu, M. Mena, E. Jnoff, N. Sun, P. Pasau, L. Ghosez, *Angew. Chem. Int. Ed.* **2009**, *48*, 5880-5883; b) Y. Watanabe, T. Washio, J. Krishnamurthi, M. Anada, S. Hashimoto, *Chem. Commun.* **2012**, *48*, 6969-6971.

[6] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758; b) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023-1052; c) N. Ye, H. Y. Chen, E. A. Wold, P. Y. Shi, J. Zhou, *Acs Infect Dis* **2016**, *2*, 382-392; d) B. Yu, D. Q. Yu, H. M. Liu, *Eur. J. Med. Chem.* **2015**, *97*, 673-698.

[7] a) Z. C. Chen, J. F. Fan, A. S. Kende, *J. Org. Chem.* **2004**, *69*, 79-85; b) E. Hayashi, S. Yamada, D. A. Brown, *Jpn. J. Pharmacol.* **1976**, *26*, P147-P147; c) S. Inoue, K. Okada, H. Tanino, K. Hashizume, H. Kakoi, *Tetrahedron* **1994**, *50*, 2729-2752; d) D. Leca, F. Gaggini, J. Cassayre, O. Loiseleur, S. N. Pieniazek, J. A. R. Luft, K. N. Houk, *J. Org. Chem.* **2007**, *72*, 4284-4287; e) L. Chen, Q. Ding, J.-J. Liu, S. Yang, Z. Zhang, in *U.S. Pat. Appl. Publ., Vol. US 20080009486*, USA, **2008**.

[8] a) G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2011**, *111*, 284-437; b) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505-2550; c) X. X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515-5546; d) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902-923; e) B. Zhao, T. P. Loh, *Org. Lett.* **2013**, *15*, 2914-2917.

[9] For an overview of *N*,*N´*-dioxide ligands and their applications in asymmetric synthesis, see: a) X. Liu, H. Zheng, Y. Xia, L. Lin, X. Feng, *Acc. Chem. Res.* **2017**, *50*, 2621-2631; b) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574-587.

[10] a) L. L. Lin, Y. L. Kuang, X. H. Liu, X. M. Feng, *Org. Lett.* **2011**, *13*, 3868-3871; b) Z. P. Yu, X. H. Liu, Z. H. Dong, M. S. Xie, X. M. Feng, *Angew. Chem. Int. Ed.* **2008**, *47*, 1308-1311; c) J. F. Zheng, L. L. Lin, K. Fu, Y. L. Zhang, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2014**, *20*, 14493-14498; d) J. F. Zheng, L. L. Lin, Y. L. Kuang, J. N. Zhao, X. H. Liu, X. M. Feng, *Chem. Commun.* **2014**, *50*, 994-996; e) J. F. Zheng, L. L. Lin, K. Fu, H. F. Zheng, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2015**, *80*, 8836-8842.

[11] At a fourteen times higher scale, a reaction of **2a** (1.05 mmol) with **3a** (0.07 mmol) deleivered **4a** in 99% yield and with 95% ee.

[12] a) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591-4597; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593-4623; c) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945-2963; d) B. M. Wang, Y. Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207-1222.

[13] a) X. Huang, K. Pham, W. B. Yi, X. F. Zhang, C. Clamens, J. H. Hyatt, J. P. Jasinsk, U. Tayvah, W. Zhang, *Adv. Synth. Catal.* **2015**, *357*, 3820-3824; b) G. L. Li, T. Liang, L. Wojtas, J. C. Antilla, *Angew. Chem. Int. Ed.* **2013**, *52*, 4628-4632.

[14] a) X. H. Liu, L. L. Lin, X. M. Feng, *Org. Chem. Front.* **2014**, *1*, 298-302; b) K. Zheng, C. K. Yin, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem. Int. Ed.* **2011**, *50*, 2573-2577; c) W. Li, X. H. Liu, X. Y. Hao, Y. F. Cai, L. Lin, X. M. Feng, *Angew. Chem. Int. Ed.* **2012**, *51*, 8644-8647.

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Asymmetric HDA Reaction

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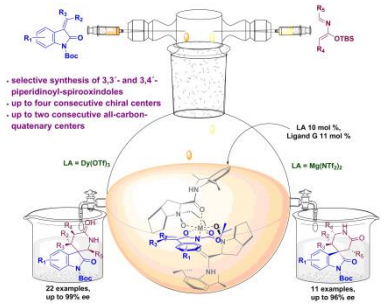
A Tunable and Enantioselective Hetero-Diels-Alder Reaction Provides Access to Distinct Piperidinoyl Spirooxindoles



Tune to Ring! Dy(III)- and Mg(II) salts with *N*,*N*-dioxide ligand catalyse enantioselective hetero-Diels-Alder reaction of silyloxy-2-azadienes with alkylidene oxindoles to selectively form 3,3´- and 3,4´-piperidinoyl- spiro-oxindoles respectively in excellent yields and with excellent enantiomeric ratios!