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Asymmetric Double Michael Reaction Catalyzed by Simple Primary Amine Catalysts: A Straightforward Approach to Construct Spirocyclic Oxindoles

Luo, Xiya[a,b](罗西娅) Wang, Liangliang[a,b](汪亮亮) Peng, Lin[a](彭林)
Bai, Jianfei[a,b](摆建飞) Jia, Lina[a,b](贾利娜) He, Guangyun[a](贺光云)
Tian, Fang[a](田芳) Xu, Xiaoying*[a](徐小英) Wang, Lixin*[a](王立新)

[a] *Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, Sichuan 610041, China*
[b] *Graduate University of Chinese Academy of Sciences, Beijing 10039, China*

The enantioselective double Michael reaction of *N*-Boc-3-nonsubstitued oxindoles with dienones catalyzed by chiral monoimide protected cyclohexane-1,2-diamines was developed. A wide range of optically active spirocyclic oxindoles were obtained up to 98% yield and up to 89% *ee*.

Keywords double Michael reaction, spirocyclic oxindole, amine catalyst, organocatalysis

Introduction

Oxindole scaffolds are versatile and useful building blocks, and commonly present in a number of natural products and biologically active molecules.[1] Particularly, spirocyclic oxindoles are attractive intermediates for the preparation of many bioactive compounds, which are widely used as drug candidates and clinical pharmaceuticals.[2] The development of highly efficient synthetic methods to access those compounds would be of great values for drug-lead synthesis. Over the past years, enormous impressive successes have been made for the preparation of those interesting structrues.[3] Among them, organocatalysis has drawn great attentions since Melchiorre disclosed the first example of organocascade reaction for the construction of spiro[4-cyclohexanone]-1,3-oxindoline.[4] And after that, Gong,[5] Chen,[6] Yuan,[7] Wang[8] and Rios[9] respectively reported excellent studies to access spirocyclic oxindoles with contiguous multiple stereocenters via asymmetric organocatalysis. It is worth mentioning that Barbas's group[10] reported a domino Michael-aldol reaction between 3-substituted oxindoles and methyleneindolinones catalyzed by a novel multifunctional organocatalyst with tertiary-primary amine and thiourea moieties, providing bispirooxindoles with over four stereocentres in good results.[10a]

Recently, our group has developed a Michael/ketone aldol/dehydration domino process of 2-hydroxy-3-acetyl indole with α,β-unsaturated ketones catalyzed by the cinchonined primary amine to create spiro[cyclohex-2-enone-oxindoles].[11a] Subsequently, we also reported a highly enantioselective double Michael reaction of 3-nonsubstitued oxindoles and dienones promoted by the cinchona-based primary amines to access spirocyclic oxindoles in excellent results.[11b] To date, asymmetric double Michael reaction of diversified donors with dienones through organocatalysis has been considered as a powerful strategy to access cyclic compouds.[12] For the significance of spirocyclic oxindoles and further expanding this useful transformation, it is still desirable to develop new catalytic system to achieve this conversion.

In the past decade, chiral amines have been widely applied in asymmetric catalysis.[13] Particularly, 1,2-diphenylethane-1,2-diamine and cyclohexane-1,2-diamine are frequently used to make chiral reagents, ligands and catalysts such as Jacobsen's salen ligands,[14] Trost's ligand,[15] and some other organocatalysts.[16] Imide monoprotected-1,2-diamines, the key intermediates in the preparation of those molecules, have been less exploited.[17] As a part of our continuous interests in chiral aminocatalysis,[18] we wish to report the double Michael reaction of 3-nonsubstituted oxindoles with dienones catalyzed by chiral monoimide-1,2-diamines.

Results and Discussion

To optimize the reaction conditions, the reaction of

* E-mail: wlxioc@cioc.ac.cn; xuxy@cioc.ac.cn; Tel.: 0086-028-85255208; Fax: 0086-028-85255208
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N-Boc-3-nonsubstituted oxindole **2a** with dienone **3a** was used as a model reaction and a series of chiral diamines were used (Figure 1). As anticipated, the reaction proceeded at room temperature in toluene and afforded the desired product in moderate yields (35%—64%) and poor enantioselectivities (Table 1, Entries 1—7). Catalysts **1f** and **1g** with diphenylethylenediamine scaffolds showed very low reactivities and gave disappointing results (Table 1, Entries 6 and 7). Catalysts **1a**—**1e** with cyclohexanediamine scaffolds afforded relatively better yields (Table 1, Entries 1—5). The reaction temperature greatly affected the effect of the catalysts (Table 1, Entries 8—12). When the reaction temperature was lowered to 0 ℃, the results were slightly improved in the presence of **1a** and **1c**. Further lowering the reaction temperature to −30 ℃, good yield and enantioselectivity were obtained (69% yield, 86% *ee*, Table 1, Entry 12).

Then a series of solvents, additives and substrate loadings were examined to further optimize the reaction conditions (Table 2). Solvents have significant effects on the results. THF, CH_3CN and halogenated hydrocarbon solvents except CH_2Cl_2 afforded trace desired products (Table 2, Entries 2, 3, 7, 8). Cyclohexane and EtOAc gave only moderate yields (Table 2, Entries 9 and 10). While aromatic hydrocarbon solvents afforded good results (69%—76% yield, 60—86% *ee*, Table 2, Entries 4—6). Among the solvents, toluene was the suitable one and gave 69% yield and 86% *ee* (Table 2, Entry 4).

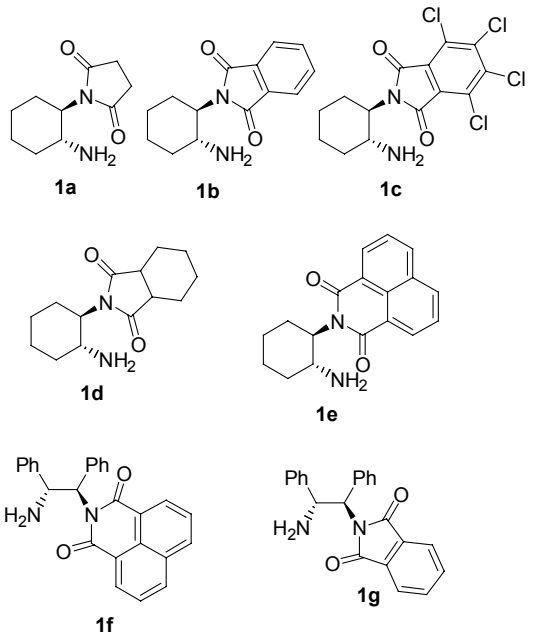
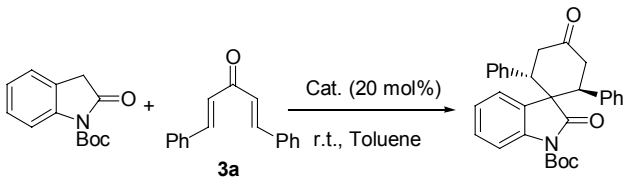


Figure 1 Structures of the catalysts.

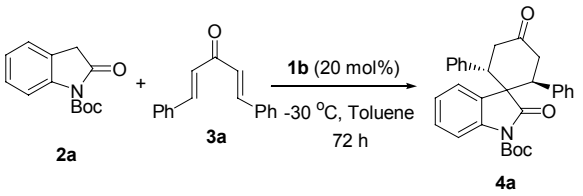
Table 1 Screening of the catalysts[a]



Entry	Cat.	Time/h	Yield[b]/%	*ee*[c]/%
1	**1a**	24	58	22
2	**1b**	24	64	11
3	**1c**	24	57	14
4	**1d**	24	56	2
5	**1e**	24	61	1
6	**1f**	24	37	4
7	**1g**	24	35	2
8[d]	**1a**	64	69	18
9[d]	**1b**	64	77	46
10[d]	**1c**	64	74	20
11[e]	**1b**	72	73	76
12[f]	**1b**	72	69	86

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol **2a**, 0.12 mmol **3a**, 20 mol% catalyst in 0.5 mL toluene at 25 ℃. [b] Isolated yield. [c] Measured by chiral HPLC and the configuration was determined by comparison with the reported data[11b] (see the supporting information). [d] The reaction was conducted at 0 ℃. [e] The reaction was conducted at −20 ℃. [f] The reaction was conducted at −30 ℃.

Table 2 Optimization of reaction conditions[a]



Entry	Solvent	Ratio of **2a**/**3a**	Yield[b]/%	*ee*[c]/%
1	CH_2Cl_2	1∶1.2	32	33
2	$CHCl_3$	1∶1.2	nd	nd
3	$ClCH_2CH_2Cl$	1∶1.2	trace	nd
4	Toluene	1∶1.2	69	86
5	*m*-xylene	1∶1.2	76	60
6	Mesitylene	1∶1.2	75	61
7	THF	1∶1.2	trace	nd
8	CH_3CN	1∶1.2	trace	nd
9	Cyclohexane	1∶1.2	41	8
10	EtOAc	1∶1.2	36	4
11	Toluene	1∶1.5	54	81
12	Toluene	1∶2	39	72
13	Toluene	1.5∶1	64	83
14	Toluene	2∶1	78	86
15[d]	Toluene	2∶1	84	86

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol **2a**, 0.12 mmol **3a**, 20 mol% **1b** in 0.5 mL toluene at −30 ℃ for 72 h. [b] Isolated yield. [c] Measured by chiral HPLC. [d] The reaction was conducted for 96 h.

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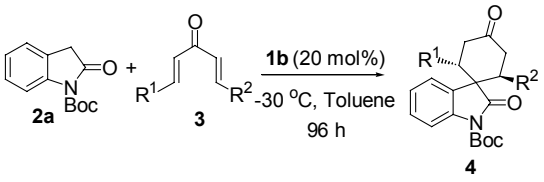
By tuning the stoichiometry of **2a** to **3a**, a significant improvement of conversion was observed (Table 2, Entries 11—14). Excessive amounts of dienones **3a** were unfavorable (Table 2, Entries 4 vs. 11 and 12). By contrast, excessive oxindole **2a** gave better yields, and slightly affected the enantioselectivties (Table 2, Entries 4 vs. 13—14). When the reaction was conducted with the molecular ratio of 2/1 reactants **2a**/**3a** in toluene at −30 ℃ for 96 h, the best result was obtained (84% yield and 86% *ee*, Table 2, Entry 15).

With the established reaction conditions, the scope of the substrates was finally investigated (Table 3). The symmetric dienones were first evaluated and afforded the desired adducts in moderate to excellent yields and enantioselectivities (up to 98% yield, up to 86% *ee*). The position of substituents on phenyl ring of dienones delivered significant influences on the enantioselectivities and yields. Unsubstituted benzene ring afforded better yield and enantioselectivity than the substituted ones (Table 3, Entry 1 vs. Entries 2—8). *ortho*-Substituent gave low yield and enantioselectivity (37% yield and 36% *ee*, Table 3, Entry 5). *para*-Substituents afforded better *ee* values than *meta*- and *ortho*-substituted ones (Table 3, Entries 2 vs. 3, 4 vs. 5, 6 vs. 7). The electronic features of the substitutents were also tested. Electron-withdrawing substituents on *para*-positions afforded better yields and enantioselectivities than electron-donating one (Table 3, Entries 2, 6 vs. 8). The electron-withdrawing substuents on *para*- and *mtea*-positions gave good to excellent yields (68%—98%). The asymmetric dienones were also tested (Table 3, Entries 9—15). Both electron-withdrawing (Table 3, Entries 9—12, 15) and electron-donating (Table 3, Entries 13—14) substituents on dienones were tolerated. Good yields and moderate to good enantioselectivities were obtained (72%—96% yield, 51%—89% *ee*), whereas low disastereoselectivities were attained except *para*-nitro group substituted (Table 3, Entries 9—14 vs. 15).

Table 3 Scope of substrate[a]



Entry	R^1	R^2	Yield[b]/%	dr[c]	ee[d]/%
1	Ph	Ph	**4a**/84	nd	86
2	4-FC_6H_4	4-FC_6H_4	**4b**/98	nd	74
3	3-FC_6H_4	3-FC_6H_4	**4c**/97	nd	55
4	3-ClC_6H_4	3-ClC_6H_4	**4d**/91	nd	48
5	2-ClC_6H_4	2-ClC_6H_4	**4e**/37	nd	36
6	4-BrC_6H_4	4-BrC_6H_4	**4f**/68	nd	83
7	3-BrC_6H_4	3-BrC_6H_4	**4g**/86	nd	60
8	4-MeC_6H_4	4-MeC_6H_4	**4h**/20	nd	59
9	Ph	3-FC_6H_4	**4i**/85[e]	1.5/1	51/53
10	Ph	4-BrC_6H_4	**4j**/83[e]	5.7/1	83/66
11	Ph	3-BrC_6H_4	**4k**/89[e]	1.8/1	73/78
12	Ph	4-$CF_3C_6H_4$	**4l**/74[e]	3.3/1	63/53
13	Ph	4-MeC_6H_4	**4m**/72[e]	1.3/1	87/83
14	Ph	3-MeC_6H_4	**4n**/96[e]	1.3/1	79/73
15	Ph	4-$NO_2C_6H_4$	**4o**/93[e]	13/1	89/82

[a] Unless otherwise noted, the reaction was conducted with 0.4 mmol **2a**, 0. 2 mmol **3**, 20 mol% **1b** in 1.0 mL toluene at −30 ℃ for 96 h. [b] Isolated yield. [c] Measured by chiral HPLC. [d] The corresponding *ee* value was measured by chiral HPLC. [e] The total yield of isomers.

Conclusions

In summary, chiral monoimide protected cyclohexane-1,2-diamines were first successfully applied to catalyze enantioselective double Michael reaction of *N*-Boc-3-nonsubstitued oxindoles and dienones and a wide range of optically active spirocyclic oxindoles were obtained up to 98% yield and up to 89% *ee*. Further studying of the catalytic mechanism of those special chiral monoimide-1,2-diamines is going on in our laboratory.

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References and Note

[1] Selected examples: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945; (b) Lin, H.; Danishefsky, S. J. *Angew. Chem.*, *Int. Ed.* **2003**, *42*, 36; (c) Ma, S.; Han, X. Q.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem.*, *Int. Ed.* **2009**, *48*, 8037.

[2] Selected examples: (a) Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. *J. Org. Chem.* **2001**, *66*, 3653; (b) Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, M. J.; Liu, J. C.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5022; (c) Zhao, L. Q.; Zhou, B.; Li, Y. Q. *Chin. J. Org. Chem.* **2011**, *31*, 553 (in Chinese).

[3] For selected reviews: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209; (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem.*, *Int. Ed.* **2007**, *46*, 8748; (c) Zhou, F.; Liu, Y. L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381; (d) Guo, H. Y.; Tian, J. J. *Chin. J. Org. Chem.* **2011**, *31,* 752.

[4] Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.; Bartoli, G.; Melchiorre, P. *Angew. Chem.*, *Int. Ed.* **2009**, *48*, 7200.

[5] (a) Chen, X. H.; Wei, Q.; Xiao, H.; Luo, S. W.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819; (b) Wei, Q.; Gong, L. Z. *Org. Lett.* **2010**, *12*, 1008.

[6] (a) Jiang, K.; Jia, Z. J.; Chen, S.; Wu, L.; Chen, Y. C. *Chem.-Eur. J.* **2010**, *16*, 2852; (b) Jiang, K.; Jia, Z. J.; Yin, X.; Wu, L.; Chen, Y. C. *Org. Lett.* **2010**, *12*, 2766.

[7] (a) Chen, W. B.; Wu, Z. J.; Pei, Q. L.; Cun, L. F.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2010**, *12*, 3132; (b) Chen, W. B.; Wu, Z. J.; Hu, J.; Cun, L. F.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2011**, *13*, 2472.

[8] (a) Jiang, X. X.; Cao, Y. M.; Wang, Y. Q.; Liu, L. P.; Shen, F. F.;

Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328; (b) Cao, Y. M.; Jiang, X. X.; Liu, L. P.; Shen, F. F.; Zhang, F. T.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124.

[9] Companyó, X.; Zea, A.; Alba, A. N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953.

[10] (a) Tan, B.; Candeias, N. R.; Barbas III, C. F. *Nature Chemistry* **2011**, *3*, 473; (b) Tan, B.; Candeias, N. R.; Barbas III, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 4672; (c) Tan, B.; Hernández-Torres, G.; Barbas III, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 12354.

[11] (a) Wang, L. L.; Peng, L.; Bai, J. F.; Huang, Q. C.; Xu, X. Y.; Wang, L. X. *Chem. Commun.* **2010**, *46*, 8064; (b) Wang, L. L.; Peng, L.; Bai, J. F.; Jia, L. N.; Luo, X. Y.; Huang, Q. C.; Xu, X. Y.; Wang, L. X. *Chem. Commun.* **2011**, *47*, 5593.

[12] (a) Li, X. M.; Wang, B.; Zhang, J. M.; Yan, M. *Org. Lett.* **2011**, *13*, 374; (b) Wu, B.; Liu, G. G.; Li, M. Q.; Zhang, Y.; Zhang, S. Y.; Qiu, J. R.; Xu, X. P.; Ji, S. J.; Wang, X. W. *Chem. Commun.* **2011**, *47*, 3992; (c) Fusco, C. D.; Lattanzi, A. *Eur. J. Org. Chem.* **2011**, 3728.

[13] For selected examples on aminocatalysis, see: (a) Bui, T.; Barbas III, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951; (b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051; (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[14] For selected reviews, see: (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063; (b) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948; (c) Loy, R. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 2786.

[15] For selected reviews, see: (a) Trost, B. M.; Vranken, D. L. V.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327; (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256; (c) Trost, B. M.; Miller, J. R.; Hoffman, C. M. *J. Am. Chem. Soc.* **2011**, *133*, 8165.

[16] (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691; (b) Nieto, S.; Lynch, V. M.; Anslyn, E. V.; Kim, H.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 9232.

[17] Kaik, M.; Gawroński, J. *Tetrahedron*: *Asymmetry* **2003**, *14*, 1559.

[18] (a) Peng, L.; Xu, X. Y.; Wang, L. L.; Huang, J.; Bai, J. F.; Huang, Q. C.; Wang, L. X. *Eur. J. Org. Chem.* **2010**, 1849; (b) Bai, J. F.; Xu, X. Y.; Huang, Q. C.; Peng, L.; Wang, L. X. *Tetrahedron Lett.* **2010**, *51*, 2803; (c) Wang, L. L.; Xu, X. Y.; Huang, J.; Peng, L.; Huang, Q. C.; Wang, L. X. *Lett. Org. Chem.* **2010**, *7*, 367; (d) Fu, J. Y.; Huang, Q. C.; Wang, Q. W.; Xu, X. Y.; Wang, L. X. *Tetrahedron Lett.* **2010**, *51*, 4870.

[19] General procedure for double Michael reaction of *N*-Boc-3-nonsubstitued oxindoles with dienones: To a stirred solution of catalyst (20 mol%) and dienones (0.2 mmol) in toluene (1.0 mL) was added oxindoles (2.0 equiv.) at −30 ℃ for 96 h. The crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give the desired product. The *ee* value was determined by HPLC analyses (for **4a**—**4d**, **4g**—**4l**, **4n** and **4o**, HPLC condition: AD-H, 1.0 mL/min, *V*(hexane)∶*V*(*i*-PrOH)=90∶10; for **4e**, HPLC condition: AD-H, 1.0 mL/min, *V*(hexane)∶*V*(*i*-PrOH)=97∶3; for **4f**, HPLC condition: AS-H, 1.0 mL/min, *V*(hexane)∶*V*(*i*-PrOH)=80∶20; for **4m**, HPLC condition: IC-H, 1.0 mL/min, *V*(hexane)∶*V*(*i*-PrOH)=95∶5).

(Pang, B.; Qin, X.)

