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Asymmetric One-Pot Sequential Mannich/Hydroamination Reaction by Organo- and Gold Catalysts: Synthesis of Spiro[pyrrolidin-3,2′-oxindole] Derivatives

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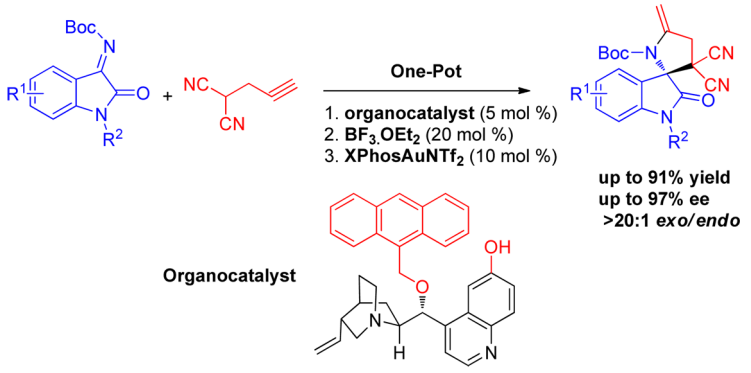
ABSTRACT



An asymmetric organo- and gold-catalyzed one-pot sequential Mannich/hydroamination reaction has been developed. Using this protocol, spiro[pyrrolidin-3,2′-oxindole] derivatives were synthesized in good yields (up to 91%) and excellent enantioselectivities (up to 97% ee).

The spiro[pyrrolidin-3,2′-oxindoles] are privileged structural motifs found in many biologically active natural and unnatural compounds (Figure 1).[1] For example, the spirooxindolones including NITD609 have emerged as a novel class of antimalarial drug candidates.[1a] Spirooxindole derivatives have also shown antitumor,[1d] anti-inflammatory,[1g] and antitubercular[1f] activities. However, synthesis of spiro[pyrrolidin-3,2′-oxindoles], for a long time, has primarily been limited to traditional cycloaddition synthetic methods, which produce racemic diastereomeric mixtures.[1b−g] To date, only a few asymmetric synthetic methods have been reported, such as those applying transition-metal catalysts, organocatalysts, and *N*-heterocyclic carbene catalysts.[2]

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Owing to its importance for the discovery of new bioactive compounds, development of new efficient methods for asymmetric synthesis of spiro[pyrrolidin-3,2′-oxindole] derivatives is of high demand.

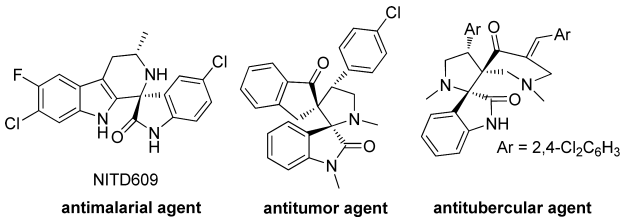


Figure 1. Examples of bioactive spiro[pyrrolidin-3,2′-oxindole] derivatives.

To achieve high efficiency in the synthesis of complex compounds, multistep sequential reactions are often employed. Inspired by recent combined uses of organo- and gold catalysts in one-pot sequential reactions,[3] we designed a new organo- and gold-catalyzed cascade protocol for the condensation of oxindole imine derivatives **1** and progargylated malononitrile **2a** (Figure 2).[4] As a result, combination of Mannich reaction and hydroamination would produce various enantiopure spiro[pyrrolidin-3,2′-oxindole] derivatives.

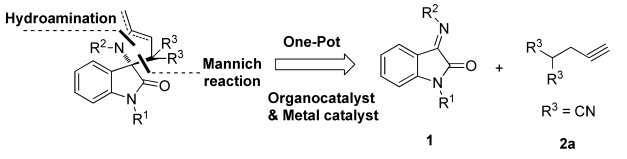


Figure 2. Designed new approach to spiro[pyrrolidin-3,2′-oxindole] derivatives.

Initially, a variety of organocatalysts (Figure 3) were evaluated for the first Mannich reaction step, and the results are summarized in Table 1. It was found that the reaction was completed smoothly in toluene at room temperature with the bifunctional thiourea catalyst **3a** in high yields but in racemic form (entry 1).[5] The enantiomeric excesses (ees) of the products were greatly improved at lower temperatures (entries 2 and 3). Change of the solvent did not affect the ee significantly (entry 4). *Cinchona*

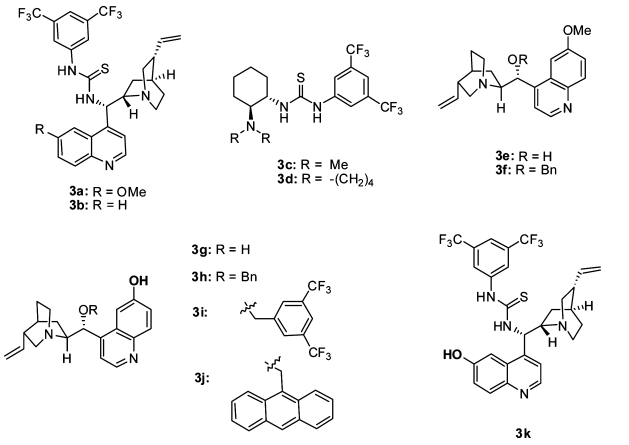
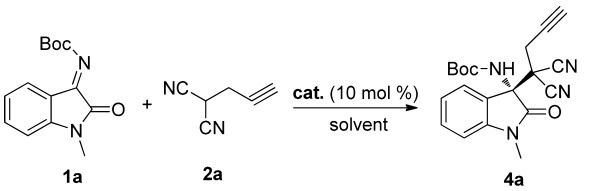


Figure 3. Screened catalysts for the Mannich reaction.

Table 1. Optimization of the Organocatalysts for the Enantioselective Addition of **2a** to **1a**[a]



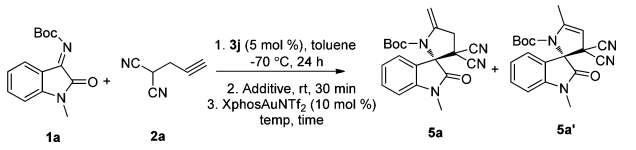
entry	catalyst	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**3a**	toluene	rt	5 min	>99	0
2	**3a**	toluene	−40	1	>99	−6
3	**3a**	toluene	−70	12	98	−42
4	**3a**	CH_2Cl_2	−70	12	54	−2
5	**3b**	toluene	−70	12	>99	−19
6	**3c**	toluene	−70	12	75	−10
7	**3d**	toluene	−70	12	36	−24
8	**3e**	toluene	−70	12	>99	14
9	**3f**	toluene	−70	12	75	35
10	**3g**	toluene	−70	12	90	44
11	**3h**	toluene	−70	24	90	75
12	**3i**	toluene	−70	12	85	83
13	**3j**	toluene	−70	18	90	95
14	**3k**	toluene	−70	12	95	−51
15[d]	**3j**	toluene	−70	24	89	95

[a] Unless otherwise noted, reactions were performed with **1a** (0.1 mmol) and **2a** (1.2 equiv) in the presence of 10 mol %of catalyst **3** in 2 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Catalyst loading (5 mol %).

(3) For a recent review for one-pot reactions with organo- and gold catalysts, see: (a) Loh, C. C. J.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 10212–10225. (b) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y.; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532. (c) Wu, H.; He, Y.-P.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 460. For selected examples of one-pot reactions using organo- and gold catalysts, see: (d) Monge, D.; Jensen, K. L.; Franke, P. T.; Lykke, L.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 9478–9484. (e) Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. *Chem.—Eur. J.* **2011**, *16*, 13409–13414. (f) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923–8926. (g) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750–1753. (h) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290–5293.

(4) For recent examples of asymmetric reactions using *N*-Boc-protected oxindole imine **1a** derivatives, see: (a) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512–2515. (b) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem.—Eur. J.* **2012**, *18*, 9276–9280. (c) Liu, Y.L.; Zhou, J. *Chem. Commun.* **2012**, 10.1039/C2CC36665G. For recent examples of asymmetric reactions using progargylated malononitrile **2a**, see: (d) Worgull, D.; Dickmeiss, G.; Jensen, K. L.; Franke, P. T.; Holub, N.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 4076–4080. (e) Zweifel, T.; Hollmann, D.; Nielsen, M.; Jørgensen, K. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1624–1629.

Table 2. Optimization for the One-Pot Synthesis of Spirooxindole **5a**[a]



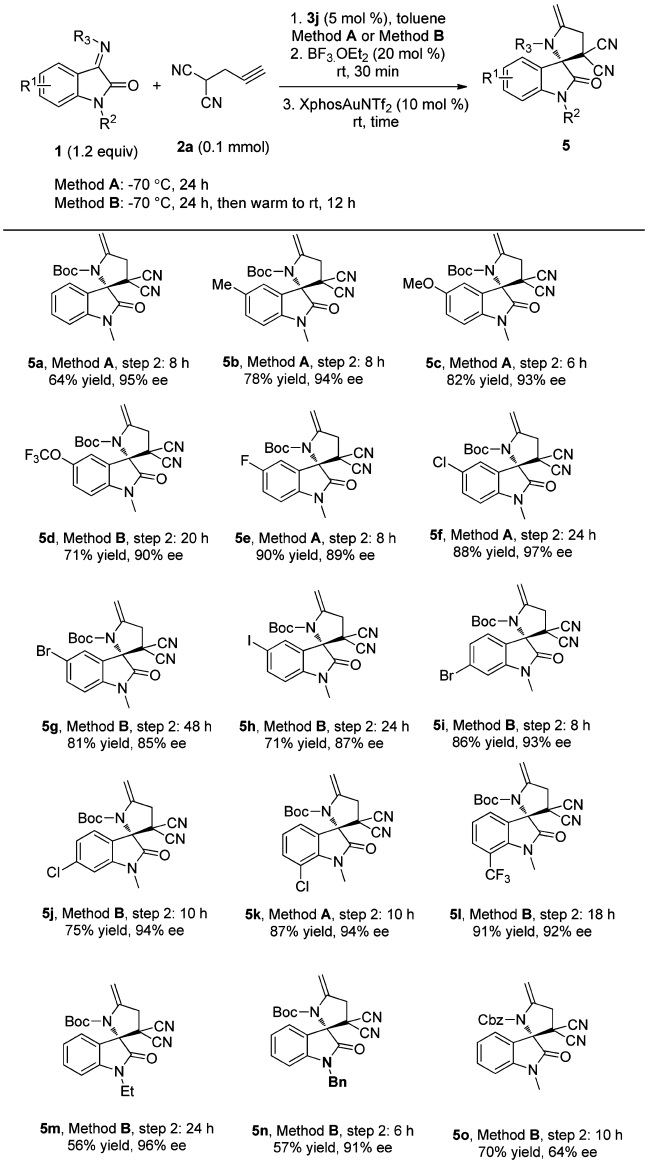
entry	additive	temp (°C)	time (h)	yield[b] (%)	*exo*/*endo* (**5a**/**5a**′)[c]	ee[d] (%)
1	none	rt	24	NR		
2	$PhCO_2H$ (10%)	rt	24	trace[e]		
3	$PhCO_2H$ (20%)	60	12	22	3:1	95
4	*p*-TsOH (10%)	rt	24	32	3.5:1	95
5	DPP (10%)	rt	24	trace[e]		
6	$BF_3 \cdot OEt_2$ (10%)	rt	24	36	>20:1	95
7	$BF_3 \cdot OEt_2$ (20%)	rt	8	53	>20:1	95
8	$BF_3 \cdot OEt_2$ (40%)	rt	8	46	>20:1	95
9[e]	**$BF_3 \cdot OEt_2$ (20%)**	**rt**	**8**	**64**	**>20:1**	**95**
10	$BF_3 \cdot OEt_2$ (20%)	60	1	50	1:3.5	95

[a] Unless otherwise noted, reactions were performed with **1a** (0.1 mmol) and **2a** (1.2 equiv) in the presence of 10 mol % of catalyst **3** in 2 mL of toluene. [b] Isolated yields. [c] Determined by ^1H NMR with crude products. [d] Determined by chiral HPLC analysis for major isomer. [e] **1a** (1.2 equiv) and **2a** (0.1 mmol) was carried out under standard conditions. DPP = diphenyl phosphate.

alkaloid catalyst **3b** and Takemoto catalyst **3c**,**d**[6] were also tested; however, poor enantioselectivities were obtained (entries 5−7). Other *Cinchona* alkaloids such as quinidine (**3e**) and quinidine derivatives (**3f**−**j**) were also investigated.[7] Catalysts **3e**−**g** gave products in good yields, though no improvement was achieved for the enantioselectivities (entries 8−10). Benzyl-substituted catalysts **3h** and **3i** gave 75% and 83% ee, respectively (entries 11 and 12). To our delight, the bulky 9-anthracenmethoxy-substituted catalyst **3j** gave excellent enantioselectivity (95% ee) (entry 13).[8] Thiourea phenol catalyst **3k** was also examined, but the ee was relatively low (−51% ee) (entry 14).[9] Lower catalyst loading (5 mol %) did not affect the yield or ee of product (entry 15).

We next examined the transformation of product **4a** into final spiro product **5a** using various metal salt catalysts, such as $AuCl_3$, $AuBr_3$, PPh_3AuCl, PPh_3AuNTf_2, $Cu(OTf)_2$, and so on.[10] The respective yields and selectivities (*endo*/*exo*)

Scheme 1. Substrate Scope of One-Pot Sequential Reaction between **1** and **2a**[a]



[a] Reactions condtions: **1** (1.2 equiv) and **2** (0.1 mmol) in toluene (2 mL), method **A** or method **B**. The *exo*/*endo* ratio of all products is >20:1. The isolated yields were given after column chromatography. The ee's were determined by chiral HPLC analysis. The absolute configuration was determined by X-ray analysis of product **5g** (see the Supporting Information), and the others were assigned accordingly.

(5) For selective examples of Mannich type reactions using *Cinchona* alkaloid thiourea catalysts, see: (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049. (b) Song, J.; Shih, H. −W.; Deng, L. *Org. Lett.* **2007**, *9*, 603–606. (c) Bai, S.; Liang, X.; Song, B.; Bhadury, P. S.; Hu, D.; Yang, S. *Tetrahedron: Asymmetry* **2011**, *22*, 518–523. (d) Nakamura, S.; Maeno, Y.; Ohara, M.; Yamaura, A.; Funahashi, Y.; Shibata, N. *Org. Lett.* **2012**, *14*, 2960–2963.

(6) For selective examples of Mannich type reactions using takemoto derivatives catalysts, see: (a) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, *16*, 2571–2575. (b) Lee, J. H.; Kim, Y. *Synthesis* **2010**, *11*, 1860–1864. (c) Enders, D.; Göddertz, D. P.; Beceño, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863–2868. (d) Zhao, D.; Yang, D.; Wang, Y.; Wang, Y.; Wang, L.; Mao, L.; Wang, R. *Chem. Sci.* **2011**, *2*, 1918–1921.

(7) For selective examples of Mannich type reactions using quinidine derivatives catalysts, see: (a) Shi, Z.; Yu, P.; Chua, P. J.; Zhong, G. *Adv. Synth. Catal.* **2009**, *351*, 2797–2800. (b) Li, L.; Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 11648–11649. (c) Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 4650–4653. (d) Liu, X.; Deng, L.; Jiang, X.; Yan, W.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 876–879. (e) Liu, X.; Deng, L.; Song, H.; Jia, H.; Wang, R. *Org. Lett.* **2011**, *13*, 1494–1497.

(8) Albertshofer, K.; Tan, B.; Barbas, C. F., III. *Org. Lett.* **2012**, *14*, 1834–1837.

(9) Zhang, T.; Cheng, L.; Hameed, S.; Liu, L.; Wang, D.; Chen, Y.-J. *Chem. Commun.* **2011**, *47*, 6644–6646.

(10) For selective reviews of hydroamination reactions, see: (a) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (c) Dion, I.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8233.

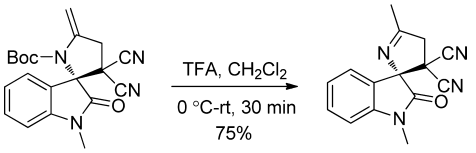
are summarized and discussed in detail in Table S1 of the Supporting Information. Fortunately, $XPhosAuNTf_2$ (XPhos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl, NTf_2 = bis(trifluoromethylsulfonyl)imide) produced **5a** in good yield (82%) with excellent selectivity (*exo*/*endo* > 20:1).[11]

We further investigated whether the spirooxindole product could be obtained by a one-pot sequential manner with combined use of organo- and gold catalysts. The results are summarized in Table 2. The initial reaction conditions did not give the derised product without any additives (entry 1). The literature mentioned that the activity of Au(I) catalyst could be inhibited by the bifunctional organocatalysts.[3b−e] Therefore, a variety of Brønsted acids were considered to be applied as the additives, including $PhCO_2H$, *p*-TsOH, DPP. When $PhCO_2H$ (10 mol %) or DPP (10 mol %) was applied at room temperature, a trace amount of product was obtained (entries 2 and 5). Higher temperature (entry 3) or use of *p*-TsOH (entry 4) gave the desired product but as a mixture of isomers in low yields. To our delight, product **5a** was obtained in 36% yield and 95% ee with 10 mol % of $BF_3\cdot OEt_2$ (entry 6). When the amount of $BF_3\cdot OEt_2$ was increased to 20 mol %, the yield of **5a** was improved to 64% yield (95% ee) (entries 7−9). Under heating conditions, a mixture of isomers (*exo*/*endo* 1:3.5) was obtained at moderate yields (entry 10).

With the optimized conditions in hand, the substrate scope was investigated (Scheme 1). Generally, moderate yields and good enantioselectivities were obtained in the presence of various substituents on the aromatic ring of oxindole imine **1**, including electron-donating groups (**5b**−**d**), withdrawing group (**5l**), and halogen substituents at various positions (**5e**−**k**). Several *N*-protecting groups were also examined. *N*-Ethyl and *N*-benzyl groups gave products **5m**,**n** in acceptable yields with excellent enantioselectivities. However, the *N*-Cbz group of imine, instead of the *N*-Boc group, gave a negative effect on the stereoselectivity (64% ee, **5o**). The absolute configuration of representative product **5g** was determined as R by single-crystal X-ray analysis (see the Supporting Information).[12]

As a further demonstration of the efficiency of this protocol, deprotection of **5a**, produced the spiro[pyrrolidin-3,2′-oxindole] derivative **6a** in 75% yield and 95% ee (Scheme 2).

Scheme 2. *N*-Boc Removal of Product **5a**



5a, 95% ee **6a, 95% ee**

In conclusion, we have successfully developed a highly efficient one-pot sequential Mannich/hydroamination reaction between oxindole imine and progargylated malononitrile by a combined use of organo- and gold catalysts. Excellent enantioselectivities (up to 97% ee) and good overall yields (up to 91%) were achieved using a quinidine phenol derivative as the organocatalyst, $XPhosAuNTf_2$ as the metal catalyst, and $BF_3\cdot OEt_2$ as the additive. This newly developed strategy has been proven to be useful for the efficient construction of biologically active spirooxindole derivatives and may be applicable to other asymmetric catalytic systems.

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Supporting Information Available. Experimental procedures and compound characterizations (^1H NMR, ^{13}C NMR, HPLC) including X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) For selective examples of hydroamination reactions using $XPhosAuNTf_2$, see: (a) Kothandaraman, P.; Mothe, S. R.; Toh, S. S. M.; Chan, P. W. H. *J. Org. Chem.* **2011**, *76*, 7633–7640. (b) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184. (c) Fustero, S.; Ibáñez, I.; Barrio, P.; Maestro, M. A.; Catalán, S. *Org. Lett.* **2013**, *15*, 832.

(12) CCDC 920347 contains the supplementary crystallographic data for **5g**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.