ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 5175–5177

www.rsc.org/chemcomm

COMMUNICATION

Organocatalytic stereocontrolled synthesis of 3,3′-pyrrolidinyl spirooxindoles by [3 + 2] annulation of isocyanoesters with methyleneindolinones†

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Received 2nd February 2012, Accepted 30th March 2012
DOI: 10.1039/c2cc30746d

A stereoselective [3 + 2] cycloaddition of isocyanoesters to methyleneindolinones catalyzed by a quinine-based thiourea-tertiary amine has been successfully developed. Just by tuning the protecting groups on substrates, a variety of optically enriched 3,3′-pyrrolidinyl spirooxindole diastereomers could be obtained in excellent enantioselectivities (up to 99% ee).

3,3′-Pyrrolidinyl spirooxindole scaffolds, extensively found in a large number of natural alkaloids and bioactive molecules, can serve as the core structural components for new pharmaceutical candidates (Fig. 1).[1] For instance, **MI-147**,[2] a rationally designed small molecule based on natural occurring Spirotryprostatin A, functions as a specific, potent inhibitor of MDM2–p53 interaction, selectively inhibiting the growth of tumor cells. Spirooxindole (−)-**1a** can directly inhibit tubulin polymerization in cells, while its enantiomer (+)-**1a** or diastereomer **1b** exhibits no bioactivity.[3] Therefore, in light of the principle of structure–activity relationship for drug design,[4] syntheses of structurally diversified and stereocontrolled 3,3′-pyrrolidinyl spirooxindoles for bioactive evaluation are highly demanded. Due to their appealing architectural complexity, chemists have developed various approaches to establish the compound libraries of 3,3′-pyrrolidinyl spirooxindole analogues.[5] Waldmann *et al.*[3] and Gong *et al.*,[6] respectively, presented a Lewis and a Brønsted acid catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides to methyleneindolinones, generating 3,3′-pyrrolidinyl spirooxindoles with high level of enantio- and diastereocontrol. Recently, Wang and Zhong[7] also disclosed an organocatalyzed Michael/cyclization sequence of isothiocyanate with methyleneindolinones, providing functionalized hetero spirooxindoles with three adjacent chiral carbon centers. Nevertheless, efficient catalytic stereoselective methods to access such a motif with two quaternary stereocenters remain rare. As a part of our persistent interest in the syntheses of optically active spirooxindoles,[8] herein, we wish to disclose the first highly enantio- and diastereoselective [3 + 2] cycloaddition involving α-substituted isocyanoesters[9] and methyleneindolinones[10] promoted by a thiourea-tertiary amine catalyst, affording 3,3′-pyrrolidinyl spirooxindoles bearing congested multiple stereogenic centers (Scheme 1).

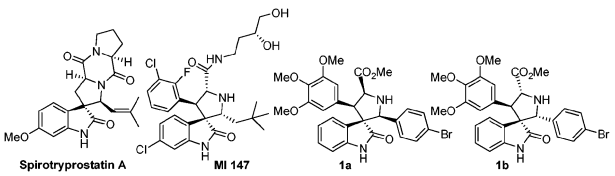
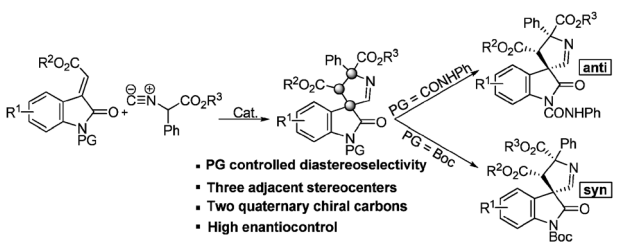


Fig. 1 Natural products and unnaturally bioactive analogues.

Diastereocontrolled synthesis in asymmetric catalysis is regarded as one of the goals for structure-oriented synthesis. To obtain diverse diastereomers, it is generally necessary to modify catalysts[11] or configuration of substrates.[12] In this study, we disclosed a novel method for stereocontrolled syntheses of 3,3′-pyrrolidinyl spirooxindole diastereomers just by tuning the protecting groups on substrates without changing the catalyst (Scheme 1).[13]

To initiate our study, *N*-phenylamide protected methyleneindolinone **3a** was selected to react with methyl α-phenylisocyano acetate **4a** catalyzed by the bifunctional thiourea-tertiary amine **2a** (Fig. 2) in DCM at room temperature (Table 1). As expected, the cycloaddition proceeded smoothly and afforded two diastereomers in moderate diastereoselectivity (2.0 : 1 dr), good yield (70% overall yield) and enantiocontrol



Scheme 1 Construction of 3,3′-pyrrolidinyl spirooxindoles by [3 + 2] cycloaddition of isocyanoesters to methyleneindolinones.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectral data of new compounds, and crystallographic data. CCDC 849672–849674. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc30746d

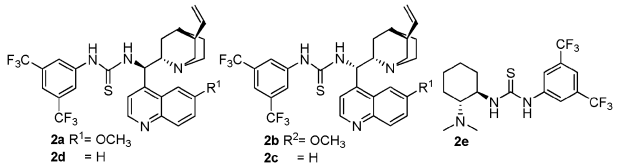
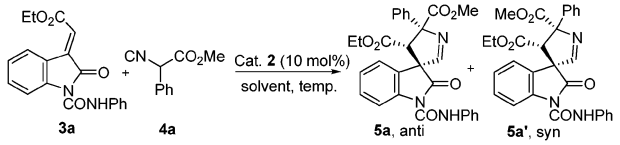


Fig. 2 Catalysts screened in this study.

Table 1 Screening of reaction conditions[a]



Entry	2	Sol.	Time/h	Yield[b] (%)	Dr[c] (5a/5a′)	Ee[d] (%)
1	**2a**	$CHCl_3$	12	70	2.0 : 1	78(72)
2[e]	**2b**	$CHCl_3$	17	64	1.3 : 1	62(57)
3[e]	**2c**	$CHCl_3$	17	63	1.6 : 1	65(72)
4	**2d**	$CHCl_3$	17	62	1.8 : 1	75(76)
5[e]	**2e**	$CHCl_3$	4	72	1.1 : 1	47(65)
6	**2a**	DCM	12	61	2.2 : 1	86(71)
7	**2a**	Toluene	12	63	1.1 : 1	81(82)
8	**2a**	THF	12	50	1 : 1	37(55)
9	**2a**	CH_3CN	8	58	1 : 3.1	8(8)
10[e]	**2a**	DMF	8	70	1 : 4.2	18(45)
11[f]	**2a**	DCM	28	71	3.9 : 1	94(81)
12[f]	**2a**	$CHCl_3$	27	82(52)[g]	3.1 : 1	95(87)

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol **3a**, 0.15 mmol **4a** and 10 mol% catalyst **2** in 0.5 mL solvent at room temperature. [b] Total yield of two diastereomers after chromatography. [c] Determined by chiral HPLC. [d] Measured by chiral HPLC; Ee value of minor diastereomers in the parentheses. [e] Contrary configuration. [f] At −20 °C and 4 Å MS (100 mg). [g] Isolated yield of the pure anti-product is given in the parentheses.

(78% ee) (Table 1, entry 1). Encouraged by this result, we then examined an array of bifunctional catalysts **2b–e** and found that quinine-based **2a** was the optimal catalyst in terms of enantio- and diastereoselectivity (Table 1, entry 1 *vs.* entries 2–5). After investigation of various reaction parameters, the optimized conditions were established to afford *anti*-**5a** in 52% yield (82% total yield), 95% ee and 3.1 : 1 dr in $CHCl_3$ at −20 °C (Table 1, entry 12).

Under the optimized conditions, the scope of substrates was evaluated, and the results are summarized in Table 2. A wide range of methyleneindolinones with a phenylamide protecting group were well tolerated and afforded the products in excellent enantioselectivities (up to 97% ee). Substituents on the aromatic ring of methyleneindolinones, regardless of the electronic nature and substituted position, provided the desired products with moderate to good yields and diastereoselectivities, and excellent enantiocontrol (Table 2, entries 2–7). With the increase of steric hindrance of the ester group on methyleneindolinone, the reactivity and diastereocontrol were slightly decreased without eroding enantioselectivity (Table 2, entry 9 *vs.* entry 8). Ethyl α-phenylisocyano acetate **4b** was also effective to deliver spirooxindoles in excellent enantioselectivities (Table 2, entries 11 and 12), while α-alkyl such as methyl and benzyl substituted isocyanoacetates were not available in this transformation due to the decreased acidity of the α-hydrogen atoms in those isocyanoesters (not shown in the table).

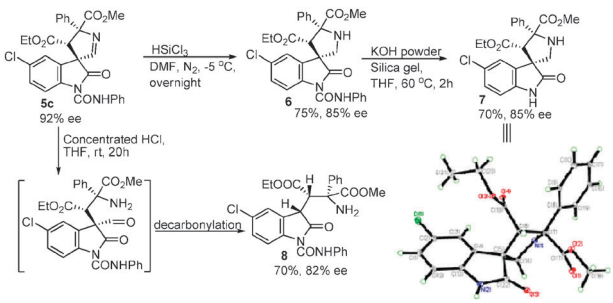
Table 2 Generality of [3 + 2] reaction with *N*-phenyl amide protected methyleneindolinones[a]

Entry	3/R[1], R[2]	4	Time/h	Yield[b] (%)	Dr[c](*anti*/*syn*)	Ee[d] (%)
1	**3a**/H, Et	**4a**	28	**5a**/60	2.7 : 1	95
2	**3b**/5-F, Et	**4a**	22	**5b**/53	6.2 : 1	92
3	**3c**/5-Cl, Et	**4a**	27	**5c**/61	7.0 : 1	92
4	**3d**/5-Br, Et	**4a**	22	**5d**/64	8.0 : 1	94
5	**3e**/5-Me, Et	**4a**	27	**5e**/61	7.2 : 1	97
6	**3f**/6-Cl, Et	**4a**	27	**5f**/53	5.1 : 1	92
7	**3g**/6-Br, Et	**4a**	27	**5g**/50	3.9 : 1	90
8	**3h**/H, Bn	**4a**	23	**5h**/45	3.2 : 1	95
9	**3i**/H, *t*Bu	**4a**	45	**5i**/41	2.8 : 1	96
10	**3a**/H, Et	**4b**	27	**5j**/41	3.0 : 1	96
11	**3d**/5-Br, Et	**4b**	22	**5k**/50	5.6 : 1	94
12	**3e**/5-Me, Et	**4b**	23	**5l**/54	3.0 : 1	95

[a] Unless otherwise noted, the reaction was conducted with 0.2 mmol **3**, 0.3 mmol **4** and 10 mol% **2a** in the presence of 4 Å MS (200 mg) in 1.0 mL $CHCl_3$ at −20 °C. [b] Isolated yield of the pure anti-product. [c] Ratio of *anti*/*syn* diastereomers; determined by ^{1}H NMR analysis of crude products. [d] Measured by chiral HPLC.

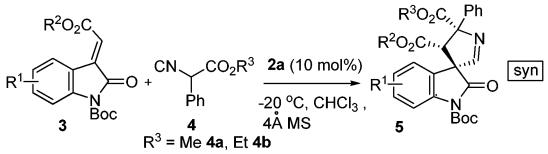
Notably, the formed cycloaddition products were highly functionalized, along with an imine moiety which provided convenience for further structural modification. As shown in Scheme 2, product **5c** was readily transformed to 3,3′-pyrrolidinyl spirooxindole **6** in good yield by transfer hydrogenation. After removal of the *N*-phenylamide group in the presence of KOH and silica gel in THF at 60 °C,[10c] spirooxindole **7** was obtained without influence of the ester groups. Unexpectedly, when **5c** was treated with concentrated hydrochloric acid, decarbonylation took place and furnished the chiral α-quaternary carbon amino acid derivative **8**. The absolute configurations of products **5a–l** were determined by X-ray analysis of compound **7**.

Interestingly, when evaluating the effect of N-protecting groups on reactivity, we observed that *N*-*tert*-butoxycarbonyl (*N*-Boc) protected methyleneindolinones reacted smoothly with isocyanoacetates and provided spirooxindoles in a switched diastereoselectivity as compared with *N*-phenylamide protected methyleneindolinones (Table 3). Remarkably, in most cases, optically pure (> 99% ee) *syn*-products could be obtained when phenylisocyano acetates **4a–b** were employed, while α-alkyl such as methyl and isopropyl substituted isocyanoacetates were



Scheme 2 Transformation of *N*-phenyl amide protected cycloadduct.

Table 3 Generality of [3 + 2] cycloaddition with Boc-protected methyleneindolinones[a]



Entry	3/R[1], R[2]	4	Time/h	Yield[b] (%)	Dr[c] (*syn*/*anti*)	Ee[d] (%)
1	**3j**/H, Et	**4a**	22	**5m**/53	3.0 : 1	99
2	**3k**/5-F, Et	**4a**	22	**5n**/56	4.9 : 1	> 99
3	**3l**/5-Cl, Et	**4a**	22	**5o**/58	4.5 : 1	99
4	**3m**/5-Br, Et	**4a**	22	**5p**/50	3.9 : 1	> 99
5[e]	**3n**/5-Me, Et	**4a**	23	**5q**/50	2.0 : 1	98
6[e]	**3o**/5-MeO, Et	**4a**	23	**5r**/45	2.3 : 1	> 99
7	**3p**/6-Cl, Et	**4a**	24	**5s**/53	4.1 : 1	98
8	**3q**/6-Br, Et	**4a**	22	**5t**/55	4.0 : 1	> 99
9	**3r**/H, Me	**4a**	22	**5u**/58	3.5 : 1	> 99
10	**3s**/H, Bn	**4a**	42	**5v**/44	2.4 : 1	> 99
11	**3t**/H, *t*Bu	**4a**	42	**5w**/50	1.9 : 1	> 99
12	**3n**/5-Me, Et	**4b**	23	**5x**/65	4.4 : 1	> 99
13	**3l**/5-Cl, Et	**4b**	22	**5y**/62	5.1 : 1	97

[a] Unless otherwise noted, the reaction was conducted with 0.2 mmol **3**, 0.22 mmol **4** and 10 mol% **2a** in the presence of 4 Å MS (200 mg) in 1.0 mL $CHCl_3$ at −20 °C. [b] Isolated yield of the pure major isomer. [c] Ratio of *syn*/*anti* diastereomers; determined by ^{1}H NMR analysis of crude products. [d] Measured by chiral HPLC. [e] 0.3 mmol **4** used.

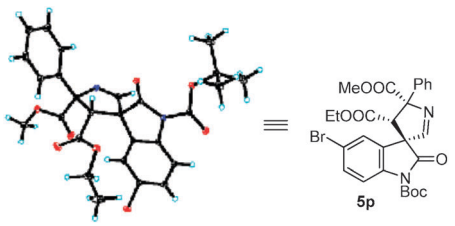


Fig. 3 X-Ray crystal structure of **5p**.

inactive in this reaction. The absolute configurations of products **5m–y** were assigned by X-ray analysis of **5p** (Fig. 3).

In summary, we have developed a novel [3 + 2] cycloaddition of isocyanoesters to methyleneindolinones and successfully obtained various optically active 3,3′-pyrrolidinyl spirooxindoles bearing multiple adjacent stereocenters. Particularly, the controlled synthesis of diastereomers could be achieved just by tuning the protecting group. The detailed survey regarding the origin of a protecting group induced diastereoselectivity switch is underway in our lab (a plausible mechanism was proposed in ESI†).

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