ORGANIC LETTERS

2010
Vol. 12, No. 13
2896−2899

Highly Diastereo- and Enantioselective Michael Additions of 3-Substituted Oxindoles to Maleimides Catalyzed by Chiral Bifunctional Thiourea−Tertiary Amine

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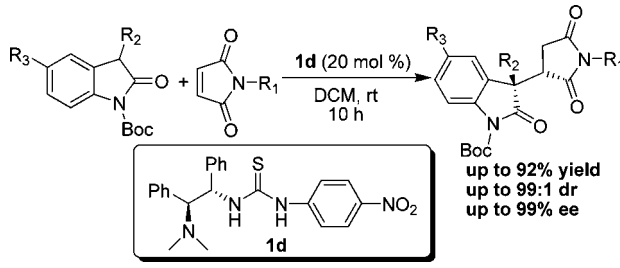
Received January 31, 2010

ABSTRACT



A highly diastereo- and enantioselective Michael addition reaction with respect to prochiral 3-substituted oxindoles and maleimides by a chiral bifunctional thiourea−tertiary amine catalyst was investigated for the first time. The corresponding adducts, containing a quaternary center at the C3-position of the oxindole as well as a vicinal tertiary center, were generally obtained in good to high yields (up to 92%) with high to excellent diastereo- (up to 99:1 dr) and enantioselectivities (up to 99% ee).

Stereoselective construction of vicinal quaternary−tertiary carbon centers not only is one of the most difficult challenges in asymmetric catalysis, but also belongs to one of the key issues that is encountered during the synthesis of complex molecules.[1] Significant effort has been directed toward to this area over the past decades.[1,2] The addition of 3-substituted oxindoles to appropriate electrophiles provides a very straightforward approach to access oxindole derivatives bearing a C3-quaternary center. In addition, chiral 3,3-disubstituted oxindoles are ubiquitous in nature and have

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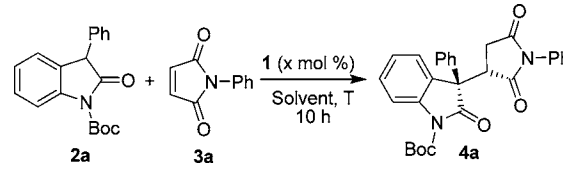
10.1021/ol100822k
Published on Web 06/08/2010

been utilized as building blocks for alkaloid synthesis.[3,4] Therefore, several methods for the synthesis of chiral 3,3-disubstituted oxindoles have been developed.[5,6] Discovering diverse electrophiles to react with 3-substituted oxindoles for the synthesis of diversely structured 3,3-disubstituted oxindoles is still strongly desired. To the best of our knowledge, some progress has been made in organic synthesis using maleimides as electrophiles reacting with various donors,[7] but the asymmetric reaction between 3-substituted oxindoles and maleimides has never been investigated. Thus, searching for a highly effective method to realize the reaction of 3-substituted oxindoles with maleimides is still challenging and interesting, as more challenging molecular complexity with vicinal quaternary−tertiary carbon centers must be created concurrently.

The past few years have witnessed a flourish of organocatalyzed reactions targeting the asymmetric formation of quaternary stereocenters.[8] Meanwhile, numerous reports on thiourea-catalyzed asymmetric C−C bond-forming reactions also have been widely published.[9] In this context, as a continuation of our studies on organocatalysis,[10] we envisioned that the asymmetric Michael reaction[11] of 3-substituted oxindoles and maleimides should be realized with some organocatalysts, giving a new range of oxindole derivatives bearing vicinal quaternary−tertiary carbon centers, Herein, we wish to describe our preliminary results.

Initially, we focused on the reaction between **2a** and *N*-phenylmaleimide (**3a**) in dichloromethane (DCM) for obtaining a set of optimal reaction conditions. As summarized in Table 1, in the presence of 5 mol % bifunctional thiourea−tertiary amines **1a**−**g** (Figure 1), respectively, it was only found that **1b** was inefficient for this model reaction (entry 2) and the other analogous organocatalysts afforded

Table 1. Screening Studies of the Optimal Reaction Conditions[a]



entry	**1**(x)	solvent	temp (°C)	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a** (5)	DCM	rt	62	70:30	78
2	**1b** (5)	DCM	rt	31	71:29	8
3	**1c** (5)	DCM	rt	52	70:30	89
4	**1d** (5)	DCM	rt	58	90:10	96
5	**1e** (5)	DCM	rt	59	63:37	96
6	**1f** (5)	DCM	rt	66	58:42	95
7	**1g** (5)	DCM	rt	57	65:35	(−) 93
8	**1h** (5)	DCM	rt	21	85:15	5
9	**1i** (5)	DCM	rt	42	45:55	5/13
10	**1j** (5)	DCM	rt	80	44:56	5/18
11	**1d** (5)	$CHCl_3$	rt	52	92:8	96
12	**1d** (5)	DCE	rt	51	90:10	96
13	**1d** (5)	*p*-xylene	rt	52	81:19	94
14	**1d** (5)	mesitylene	rt	52	87:13	95
15	**1d** (5)	THF	rt	47	85:15	11
16	**1d** (5)	CH_3CN	rt	47	80:20	47
17	**1d** (5)	Et_2O	rt	39	87:13	83
18	**1d** (5)	DMF	rt	16	80:20	10
19	**1d** (5)	DCM	0	74	93:7	93[e]
20	**1d** (5)	DCM	−20	67	92:8	94[f]
21	**1d** (5)	DCM	−40	62	95:5	95[g]
22	**1d** (5)	$CHCl_3$	45	68	88:12	94[h]
23	**1d** (10)	DCM	rt	73	92:8	96[i]
24	**1d** (20)	DCM	rt	91	95:5	97[i]

[a] Unless otherwise noted, reactions were carried out with **2a** (0.2 mmol), **3a** (0.24 mmol), and appropriate catalyst **1** in 1.0 mL of solvent for 10 h. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral-HPLC analysis. [e] Run for 18 h. [f] Run for 20 h. [g] Run for 24 h. [h] Run for 6 h. [i] 1.5 equiv of **3a** was used.

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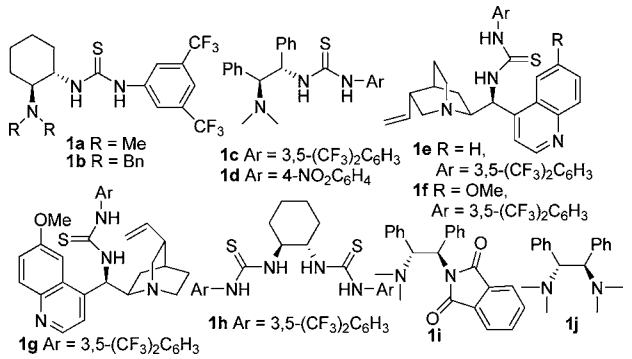


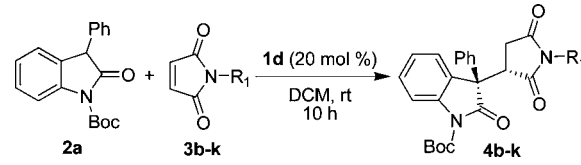
Figure 1. Chiral organocatalysts screened in this work.

moderate yields and high diastereo- and enantioselectivities at room temperature (entries 1 and 3−7). In addition, we also investigated organocatalysts **1h**−**j** but achieved very poor enantioselectives (entries 8−10). Consequently, the survey of organocatalysts **1a**−**j** (Figure 1) revealed that the dual functionality of chiral thiourea tertiary-amine bearing thiourea and tertiary amine was crucial to the diastereo- and enantioselectivity of this Michael addition. By all accounts, **1d** turned out to be the most effective catalyst for this transformation (entry 4).[12] Then, screening of solvents reveled that slight variations in diastereoselectivity and significant solvent-dependent in enantioselectivity were observed (entries 4 and 11−18). Despite a similar level of dr values for these solvent, very high ee values in chlorinated solvents (entries 4, 11, and 12), xylene (entry 13), and mesitylene (entry 14) were obtained. At the same time, a good ee value in diethyl ether (entry 17) and poor ee values in THF (entry 15), CH_3CN (entry 16), and DMF (entry 18) were also observed. Thus, in an overall consideration of reactivity, yield, dr, and ee, DCM was chosen as the optimal solvent (entry 4). Afterward, lowering the reaction temperature caused slightly decreased ee values and prolonged reaction times (entries 4 vs 19−21). In contrast, when the reaction was carried out in CH_3Cl at 45 °C, it was found that the reaction was complete in 6 h and gave 94% ee for the major isomer, but the dr value decreased to 88:12 (entry 22). To our delight, further optimization of catalyst loading revealed that 20 mol % of **1d** was able to afford the best yield (entries 23 and 24). On the basis of these results, a set of optimal reaction conditions were screened out: 0.2 mmol **2a** and 1.5 equiv of **3a** in 1.0 mL of DCM with 20 mol % of **1d** as catalyst at room temperature.

With the optimal reaction conditions in hand, the generality of the Michael reaction with respect to *N*-Boc-3-phenyloxindole (**2a**) and various maleimides **3** was first investigated. As shown in Table 2, a wide range of *N*-aromatic and *N*-aliphatic maleimides worked well with **2a**, and the reaction tolerated a number of functional groups on the electrophile. For maleimide derivatives **3b**−**h** with either electron-donating or electron-withdrawing substituents on the phenyl ring, the reaction smoothly gave the desired products in high diastereoselectivity and high to excellent enantioselectivity (92−98% ee) for the major isomer (entries 1−7). For the *N*-linear and *N*-branched aliphatic substrates **3i**−**k**, the reaction also provided the corresponding products with high dr and ee values but moderate yields (entries 8−10).

Subsequently, the scope of the Michael reaction with respect to various *N*-Boc-3-substituted oxindoles **2b**−**k** and *N*-phenyl maleimide (**3a**) or *N*-*p*-chlorophenyl maleimide (**3c**) was also examined (Table 3). Generally, the desired

Table 2. Asymmetric Michael Reaction of *N*-Boc-3-phenyloxindole (**2a**) and Different *N*-Substituted Maleimides[a]



entry	**3**	R_1	**4**	yield[b] (%)	dr[c]	ee[d] (%)
1	**3b**	4-BrC_6H_4	**4b**	89	91:9	98
2	**3c**	4-ClC_6H_4	**4c**	74	94:6	96
3	**3d**	4-$CH_3C_6H_4$	**4d**	92	96:4	97
4	**3e**	3-ClC_6H_4	**4e**	82	92:8	94
5	**3f**	3-BrC_6H_4	**4f**	68	82:18	92[e]
6	**3g**	3-$MeOC_6H_4$	**4g**	92	95:5	96
7	**3h**	3,4-$Cl_2C_6H_3$	**4h**	50	87:13	94
8	**3i**	*c*-hexyl	**4i**	65	89:11	86
9	**3j**	*i*-propyl	**4j**	45	94:6	85
10	**3k**	allyl	**4k**	64	89:11	91

[a] Reaction conditions: **2a** (0.2 mmol), **3** (0.3 mmol), **1d** (0.04 mmol %), and CH_2Cl_2 (1.0 mL) at rt for 10 h. [b] Isolated yields. [c] Determined by ^1H NMR. [d] Determined by chiral-HPLC analysis. [e] The absolute configuration of **4f** was determined by X-ray analysis; it contains a (C7*R*, C20*S*) configuration (see the Supporting Information). The other products of this paper were assigned by analogy.

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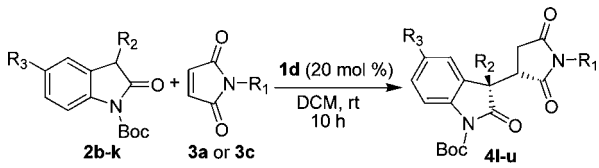
Table 3. Asymmetric Michael Reaction of Different 3-Substituted Oxindoles to Maleimides **3a** or **3c**[a]



2b R_2 = 4-MeC_6H_4, R_3 = H
2c R_2 = 4-PhC_6H_4, R_3 = H
2d R_2 = 4-FC_6H_4, R_3 = H
2e R_2 = 3,5-$Me_2C_6H_3$, R_3 = H
2f R_2 = Ph, R_3 = F
2g R_2 = *i*-propyl, R_3 = H
2h R_2 = 4-$MeOC_6H_4$, R_3 = H
2i R_2 = Bn, R_3 = H
2j R_2 = Ph, R_3 = Me
2k R_2 = *n*-Bu, R_3 = H

entry	2	3	4	yield[b] (%)	dr[c]	ee[d] (%)
1	**2b**	**3a**	**4l**	86	92:8	95
2	**2c**	**3a**	**4m**	87	94:6	97
3	**2d**	**3a**	**4n**	80	94:6	95
4	**2e**	**3a**	**4o**	81	92:8	99
5	**2f**	**3a**	**4p**	90	92:8	96
6	**2g**	**3a**	**4q**	67	99:1	94[e]
7	**2h**	**3c**	**4r**	75	90:10	94
8	**2i**	**3c**	**4s**	87	63:37	94
9	**2j**	**3c**	**4t**	73	90:10	96
10	**2k**	**3c**	**4u**	65	95:5	97[f]

[a] Reaction conditions: **2a** (0.2 mmol), **3** (0.3 mmol), **1d** (0.04 mmol %), and CH_2Cl_2 (1.0 mL) at room temperature for 10 h. [b] Isolated yields. [c] Determined by ^1H NMR. [d] Determined by chiral-HPLC analysis. [e] Run for 36 h. [f] Run for 24 h.

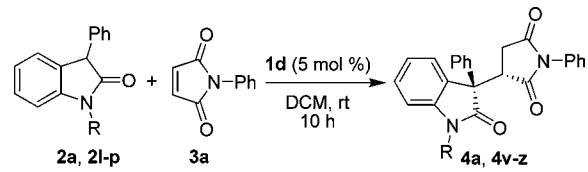
oxindole products bearing various substituents at C3-position were obtained in moderate to good yields with good to excellent dr and ee. In most cases, more than 90:10 dr values were observed (entries 1−7, 9, and 10). In the only one exceptional case, moderate dr (63:37) was provided in the addition of **2i** to **3c** (entry 8). It should be noted that, for the above-surveyed cases, all of the major isomeric products **4l**−**u** exhibited greatly satisfied ee values (94−99%).

Additionally, we also examined the effects of *N*-protection group of oxindole. As shown in Table 4, under the same reaction conditions, *N*-unprotected (entry 2), *N*-methyl (entry 3), and *N*-benzyl (entry 4) decreased the reaction rate. At the same time, *N*-carbethoxy (entry 5) and *N*-acetyl (entry 6) protected substrates provided poor results. However, in sharp contrast, *N*-Boc-oxindole **2a** gave the desired product with acceptable results (entry 1). This indicates the *N*-Boc group is crucial for the reactivity and stereocontrol.

Notably, another electrophile, maleic anhydride, was also attempted in this study with **1a** as catalyst (Figure 2). To our delight, the addition reactions of oxindoles **2d** and **2b** to maleic anhydride using **1a** proceeded smoothly (see the Supporting Information) and provided the desired products in good yields with good diastereo- and enantioselectivites (**5a**: 71% yield, 94:6 dr and 85% ee; **5b**: 76% yield, 95:5 dr and 85% ee).

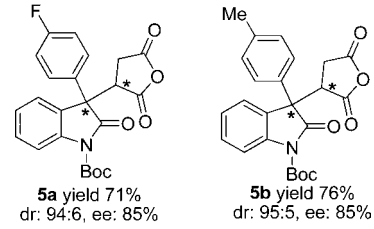
In summary, we have developed a highly diastereo- and enantioselective Michael addition reaction with respect to

Table 4. Examination of the Effects of *N*-Protection Group of Oxindole[a]



entry	R	4	yield (%)	dr	ee (%)
1	Boc (**2a**)	**4a**	58	90:10	96
2	H (**2l**)	**4v**	trace		
3	Me (**2m**)	**4w**	nr[b]		
4	Bn (**2n**)	**4x**	nr[b]		
5	EtOCO (**2o**)	**4y**	60	63:37	16/4
6	Ac (**2p**)	**4z**	36	53:47	1/1

[a] The same reaction conditions as in Table 1, entry 4. [b] nr = no reaction.



5a yield 71%
dr: 94:6, ee: 85%

5b yield 76%
dr: 95:5, ee: 85%

Figure 2. Experimental results with maleic anhydride as electrophile.

prochiral 3-substituted oxindoles and maleimides by a chiral bifunctional thiourea−tertiary amine catalyst. The high stereoselectivity and very broad substrate scope of this reaction make it potentially useful in the synthesis of a new range of oxindole derivatives. The desired products of this reaction, containing a quaternary center at the C3-position of the oxindole as well as a vicinal tertiary center that are readily obtained via this viable approach, are difficult to access through other methods. Investigations are ongoing in our laboratory to utilize versatile oxindoles as nucleophiles with chiral organocatalysts for asymmetric catalysis.

Acknowledgment. We are grateful for financial support from the NSFC (No. 20802074) and the National Basic Research Program of China (973 Program) (2010CB833300).

Supporting Information Available: Experimental procedures, spectral data, X-ray crystal structure, and a CIF. This information is available free of charge via the Internet at http://pubs.acs.org.

OL100822K