Tetrahedron 70 (2014) 3478–3484

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient asymmetric Michael reaction of 2-oxindole-3-carboxylate esters with maleimides catalyzed by cinchonidine

Jing Zhou[a,b], Li-Na Jia[a,b], Lin Peng[a], Qi-Lin Wang[a,b], Fang Tian[a], Xiao-Ying Xu[a,*], Li-Xin Wang[a,*]

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

ARTICLE INFO

Article history:
Received 15 December 2013
Received in revised form 9 March 2014
Accepted 19 March 2014
Available online 26 March 2014

Keywords:
2-Oxindole-3-carboxylate esters
Maleimides
Michael reaction
Cinchonidine

ABSTRACT

A highly efficient enantioselective Michael reaction of 2-oxindole-3-carboxylate esters with *N*-maleimides catalyzed by commercially available cinchonidine was described. The desired adducts, containing a quaternary center at the C3-position and a vicinal tertiary center, were obtained in excellent yields (up to 99%), good enantioselectivities (up to 85% ee), and diastereoselectivities (dr>90:10) in the presence of 0.05–5 mol % catalyst loading.

1. Introduction

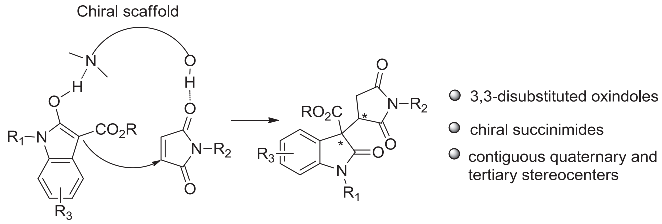
Optically active 3,3-disubstituted oxindole skeletons constitute important structural motifs in a variety of natural products and biologically active drugs.[1] For the significance of those molecules, a variety of organocatalytic asymmetric protocols have been developed, such as Michael additions,[2] aldol reactions,[3] Mannich reactions,[4] alkylations,[5] aminooxygenations[6] etc. Among them, Michael addition of 3-substituted oxindoles to appropriate electrophiles has been considered as a generally applied and feasible way to access chiral 3,3-disubstituted oxindoles.[7] Additionally, maleimides have been extensively applied in asymmetric organocatalysis to construct chiral succinimide derivatives, which are core structural units found in natural products and some clinical drug candidates.[8] As a result, the addition of 3-substituted oxindoles to maleimides has drawn chemists' attentions. In 2010, Yuan and coworkers first reported Michael addition of 3-substituted oxindoles to *N*-maleimides catalyzed by chiral tertiary amine thioureas in excellent results.[2g] Later, bicyclic guanidines[9] and didodecyl prolinol TMS-ether[10] were also used in this transformation. All the reported strategies involved only 3-alkyl- or 3-aryl-substituted oxindoles and more than 10 mol % catalyst was needed in most cases. To the best of our knowledge, the reaction of 3-carboxylate esters substituted oxindoles with maleimides has not been reported.[11] It is still desirable and useful to develop new protocols catalyzed by simple, cheap, commercially available catalysts to afford new kinds of chiral 3,3-disubstituted oxindoles with succinimides and adjacent quaternary and tertiary stereocenters.

Over the past decades, cinchona alkaloids are widely used as chiral organic catalysts in asymmetric catalysis. In our previous work, we have successfully applied cinchona alkaloids and their derivatives in some asymmetric catalyses, especially in asymmetric Michael addition and cyclization of maleimides,[12] and for the construction of oxindole motifs with quaternary stereocenters.[13] Inspired by those achievements, we envisioned that the addition of 3-carboxylate ester substituted oxindoles to maleimides may be realized in the presence of cinchona alkaloids, in which the tertiary amine group would activate the oxindoles and the hydroxyl group would activate the maleimides through hydrogen bondings. Thus the synergistic interactions would ensure high stereoselectivity, affording the corresponding optically active 3,3-disubstituted oxindoles with contiguous quaternary and tertiary stereocenters (Scheme 1). As a part of our continuing interests in asymmetric syntheses,[14] herein, we wish to report the first asymmetric Michael addition of 3-carboxylate ester substituted oxindoles to maleimides catalyzed by simple and commercially available cinchona alkaloids (Fig. 1).

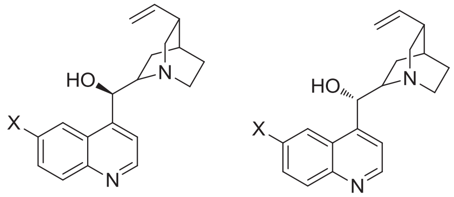
---

* Corresponding authors. Tel./fax: +86 28 85255208; e-mail addresses: wlxioc@cioc.ac.cn (L.-X. Wang), xuxy@cioc.ac.cn (X.-Y. Xu).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.065



Scheme 1. Strategy for the construction of 3,3-disubstitued oxindoles.



Cinchonine **3a**, X= H Cinchonidine **3b**, X= H

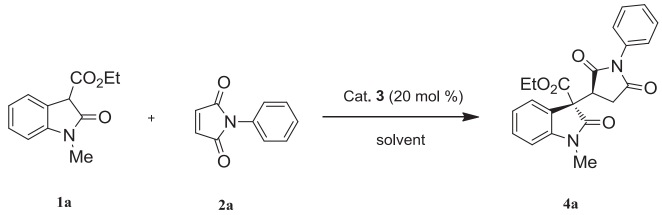
Quinine **3c**, X = OMe Quinidine **3d**, X= OMe

Fig. 1. Screened catalysts.

2. Results and discussion

The initial investigation to validate our hypothesis started with the reaction of 2-oxindoline-3-carboxylate **1a** with *N*-phenyl maleimide **2a** catalyzed by 20 mol % cinchonine in DCM at room temperature. The reaction took place smoothly to afford the desired product in 95% yield and 55% ee (Table 1, entry 1). Inspired by this result, a series of solvents were investigated and the results were listed in Table 1. This transformation was carried out well in all solvents except strong polar solvent DMF and gave good to excellent yields (64–98%) and moderate enantioselectivities (45–58% ee). Halohydrocarbon and hydrocarbon solvents such as CH_2Cl_2, $CHCl_3$, toluene gave moderate enantioselectivities (53–58% ee, Table 1, entries 1–6), and strong polar solvent DMF gave poor enantioselectivity (10% ee, Table 1, entry 11). $CHCl_3$ gave the highest enantioselectivity with excellent yield (58% ee, 96% yield, Table 1, entry 2) and was chosen as the most suitable solvent. Other commercially available cinchona alkaloids were also evaluated in $CHCl_3$. Cinchonidine turned out to be the most effective catalyst with 99% yield and 63% ee (Table 1, entry 12). Further improvement could be achieved by lowering the reaction temperature (Table 1, entries 15–17). On lowering the temperature to −35 °C, the enantioselectivity increased to 73% ee with 99% yield in an acceptable reaction time (Table 1, entry 17).

Table 1
Optimization of reaction conditions[a]

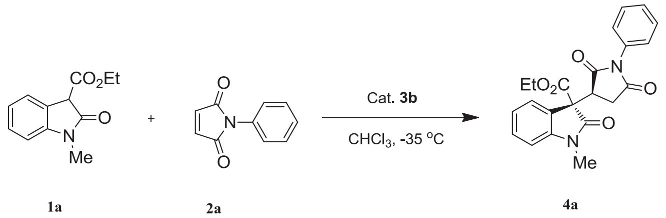


Entry	Cat.	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	CH_2Cl_2	25	2	95	83:17	55[e]
2	**3a**	$CHCl_3$	25	2	96	80:20	58[e]
3	**3a**	DCE	25	2	98	82:18	55[e]
4	**3a**	Cyclohexane	25	2	72	79:21	53[e]
5	**3a**	$PhCH_3$	25	2	97	76:24	54[e]
6	**3a**	Mesitylene	25	2	95	77:24	53[e]
7	**3a**	Et_2O	25	2	89	76:25	57[e]
8	**3a**	THF	25	2	97	74:26	52[e]
9	**3a**	EtOAc	25	2	92	75:25	50[e]
10	**3a**	CH_3CN	25	2	64	78:22	45[e]
11	**3a**	DMF	25	2	34	52:48	10[e]
12	**3b**	$CHCl_3$	25	2	99	80:20	63
13	**3c**	$CHCl_3$	25	2	99	75:25	53
14	**3d**	$CHCl_3$	25	2	99	72:28	48[e]
15	**3b**	$CHCl_3$	50	1	97	79:21	60
16	**3b**	$CHCl_3$	−15	5	99	82:18	68
17	**3b**	$CHCl_3$	−35	13	99	88:12	73

[a] Unless otherwise noted, reactions were conducted with 0.2 mmol **1a**, 0.2 mmol **2a**, 20 mol % **3**, in 1.0 mL solvent.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] The major diastereomers, determined by chiral HPLC analysis.
[e] Contrary configuration.

To further improve the enantioselectivity, molar ratio, concentrations of reactants and catalyst loadings were studied, and the results were presented in Table 2. Increasing or lowering the molar ratio significantly increased the reaction rate, while slightly affected the dr and ee values (Table 2, entries 1 and 2). Increasing or lowering the concentration of substrates has slight effect on the reaction time, yields, and enantioselectivities (Table 2, entries 3 and 4). The enantioselectivity could be further improved to 75% ee with 5 mol % catalyst **3b** (Table 2, entry 5), and further lowering the catalyst loading decreased the enantioselectivities. It was worth noting that the introduction of carboxylate substituents at C3-position of oxindoles greatly increased the reactivity and only 0.05 mol % **3b** was sufficient to afford the reaction in high yield (99%) with 68% ee (Table 2, entry 9).[2g,9–11] On the basis of those screenings, a set of optimal reaction conditions were established: 0.2 mmol **2a** and 0.2 mmol **3a** in 1.0 mL $CHCl_3$ with 5 mol % of cinchonidine at −35 °C.

Table 2
Optimization of reaction conditions[a]



Entry	Cat. loading (mol %)	**1a/2a**	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	20	1:2	1	94	89:11	74
2	20	2:1	1	99	89:11	74
3[e]	20	1:1	15	99	89:11	73
4[f]	20	1:1	15	97	89:11	75
5	5	1:1	18	93	89:11	75
6	0.5	1:1	24	92	89:11	73
7	0.1	1:1	5 days	99	88:12	72
8	0.05	1:1	10 days	56	81:19	55
9	0.05	1:2	8 days	99	87:13	68

[a] Unless otherwise noted, reactions were conducted with 0.2 mmol scale, and catalyst **3b** in $CHCl_3$ (1.0 mL).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] The major diastereomers, determined by chiral HPLC analysis.
[e] 0.5 mL $CHCl_3$ was used.
[f] 2.0 mL $CHCl_3$ was used.

Under the optimal reaction conditions, the generality of **1a** and various maleimides **2** was further studied and the results were listed in Table 3. A wide range of *N*-aromatic (**2a–i**) and aliphatic (**2j–l**) maleimides worked well with **1a**, and all the cases afforded excellent yields and moderate to good enantioselectivities (93–99% yield, 63–85% ee). *N*-Aliphatic maleimides afforded relatively higher enantioselectivity compared with their *N*-aromatic counterparts (Table 3, entries 10–12 vs 1–9).