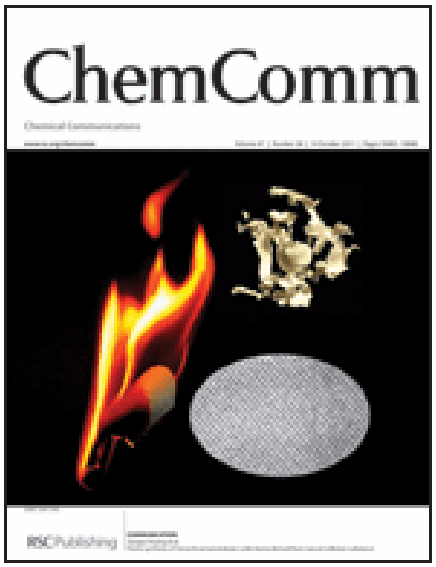

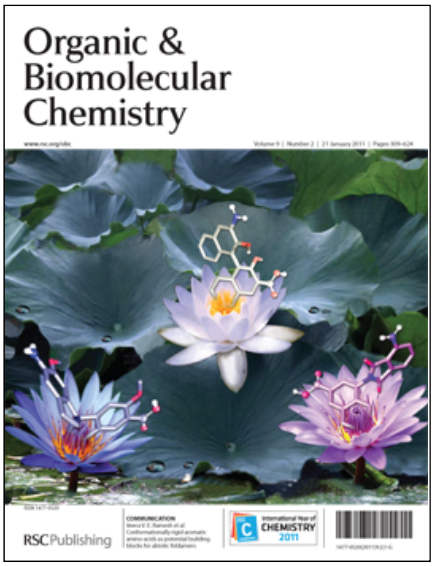

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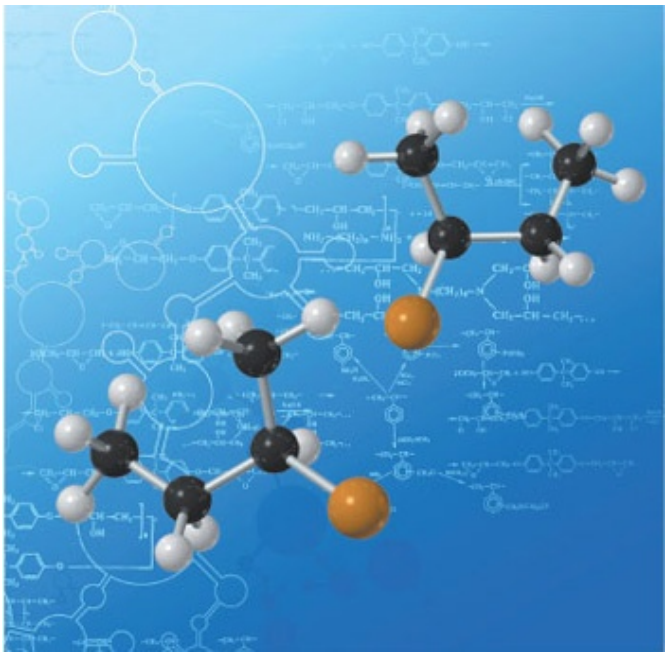

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COMMUNICATION

Direct asymmetric Mannich reaction of phthalides: facile access to chiral substituted isoquinolines and isoquinolinones†‡

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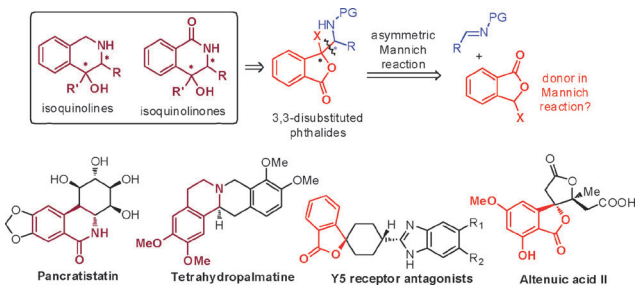
The first Mannich reaction employing phthalides using a quinidine-based multifunctional catalyst has been developed. The reported method led to the synthesis of 3,3-disubstituted phthalide derivatives in excellent yields, with good diastereo- and enantioselectivities. Convenient synthesis of chiral isoquinolinones and isoquinolines has also been demonstrated.

Substituted isoquinolines and isoquinolinones are useful building blocks in organic synthesis due to their structural importance, chemical stability and relative accessibility. Furthermore, such structures display a broad spectrum of biological properties, and they are widely present in many bioactive molecules and natural products (Scheme 1).[1] In spite of broad interest in chemical preparation of isoquinolines and isoquinolinones,[2] synthetic methods to access chiral derivatives of these molecules are very limited. One common approach was to utilize a tandem 1,2-addition–cyclization sequence to construct the isoquinoline or isoquinolinone core, and a stoichiometric amount of a chiral imine was typically employed in such an approach.[3] Another strategy, in which optically pure amino acids were used as starting materials, has found limited applications.[4] To the best of our knowledge, catalytic asymmetric synthesis of optically enriched substituted isoquinolinones and isoquinolines remains elusive. An efficient method to access these biologically and synthetically significant molecules is certainly of enormous importance.



Scheme 1 Selected examples of biologically important isoquinolines, isoquinolinones, phthalides and the projected Mannich reaction.

To derive optically enriched isoquinolinones, we reasoned that chiral 3,3-disubstituted phthalides could serve as a convenient precursor. It is noteworthy that 3,3-disubstituted phthalides[5] are also molecules of biological significance (Scheme 1), and thus methods for their asymmetric preparation are highly desired. As shown in Scheme 1, 3,3-disubstituted phthalides with a β-amino group are anticipated to undergo intramolecular cyclization smoothly to afford isoquinolinones, and we envisioned that such phthalide structures may be prepared *via* a direct Mannich reaction between activated phthalides and imines. Up to the present time, utilization of phthalide derivatives in direct Mannich reaction is unknown. We envisioned that installation of an activating group at the 3-position of phthalides may render them enhanced reactivities suitable for the direct Mannich reaction. It should be noted that such reactions of phthalides are versatile and powerful in constructing molecules of biological significance; in addition to the substituted phthalide products bearing a quaternary stereogenic center,[6] optically enriched isoquinolinones and isoquinolines are also readily attainable.

Organic catalysts containing a tertiary amine group and a Brønsted acid moiety seem to be appropriate for both substrate activations and stereochemical control in the projected Mannich reaction. Therefore, a number of bifunctional and trifunctional catalysts were prepared and screened for the Mannich reaction of phthalide derivative **1** with imine **2** (Table 1). L-Tryptophan-derived **Trp-1**[6k] was able to promote the reaction, however, the stereoselectivity was poor (entry 1). Quinidine-derived sulfonamide **QD-1**[6j] was ineffective (entry 2), and *Cinchona* alkaloid-based tertiary amine–thioureas **QD-2** and **Q1** also had low catalytic activities (entries 3 and 4). Trifunctional catalysts[6f] with amino acid residue incorporated were next examined. Combination of quinine with L-valine and L-isoleucine did not yield effective catalysts (entries 5 and 6). On the other hand, when D-valine was incorporated into the catalyst structure (**QD-5**), a marked increase in enantioselectivity was observed (entry 7), suggesting the importance of chirality matching between amino acids and *Cinchona* alkaloids. We were prompted to explore more extensively the different combinations of these two privileged chiral scaffolds. Insertion of L-*tert*-leucine into cinchonine or quinine yielded a promising catalyst, whereas a quinine-based

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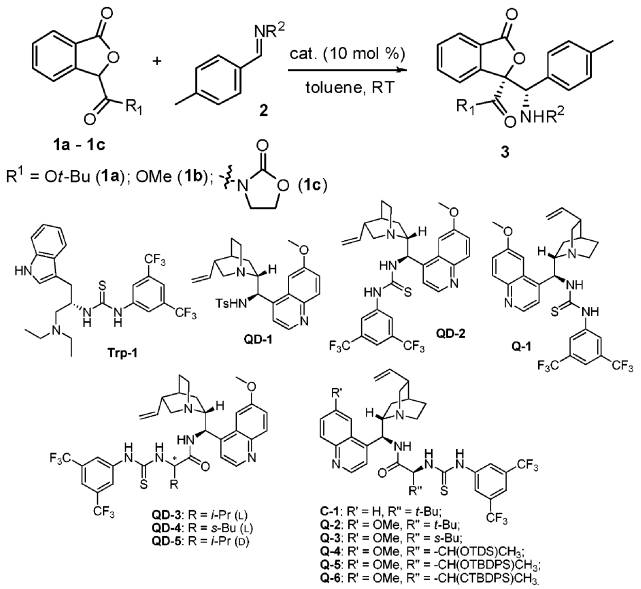
Table 1 Catalyst screening for asymmetric Mannich reaction of **1** and **2**[a]



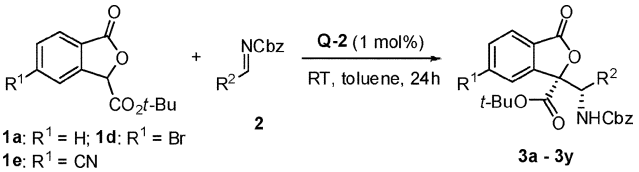
Entry	1	R^2	Catalyst	Yield[b]/%	dr[c]	ee[d]/%
1	**1a**	Boc	**Trp-1**	89	78 : 22	39
2	**1a**	Boc	**QD-1**	< 50	—	—
3	**1a**	Boc	**QD-2**	91	79 : 21	27
4	**1a**	Boc	**Q-1**	92	77 : 23	40
5	**1a**	Boc	**QD-3**	86	77 : 23	−5
6	**1a**	Boc	**QD-4**	87	74 : 26	−11
7	**1a**	Boc	**QD-5**	90	69 : 31	62
8	**1a**	Boc	**C-1**	88	61 : 39	82
9	**1a**	Boc	**Q-2**	85	63 : 37	83
10	**1b**	Boc	**Q-2**	91	55 : 45	80
11	**1c**	Boc	**Q-2**	< 50	—	—
12	**1a**	Cbz	**Q-2**	93	87 : 13	92
13	**1a**	Bz	**Q-2**	96	77 : 23	29
14	**1a**	Cbz	**Q-3**	92	86 : 14	89
15	**1a**	Cbz	**Q-4**	90	89 : 11	71
16	**1a**	Cbz	**Q-5**	88	85 : 15	79
17	**1a**	Cbz	**Q-6**	88	88 : 12	70
18[e,f]	**1a**	Cbz	**Q-2**	90	88 : 12	95

[a] Reactions were carried out using **1** (0.05 mmol), **2** (0.06 mmol), the catalyst (0.005 mmol) in toluene (0.1 mL) at room temperature. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by HPLC analysis on a chiral stationary phase. [e] With 1 mol% catalyst. [f] The reaction was performed in 0.5 mL solvent.

catalyst gave slightly better results (entries 8 and 9). We next focused on tuning the two reaction partners to further improve the stereoselectivities. Variation of the phthalide ester moiety led to no improvement (entries 10 and 11). The utilization of *N*-Cbz imine greatly enhanced the reaction, and good diastereoselectivity and excellent enantioselectivity were attainable (entry 12). Furthermore, we tested a number of quinine-based trifunctional catalysts with different amino acid residues, and **Q-2** still stood out to be the best catalyst (entries 14–17). To make the method more practical and economical, catalyst loading was further decreased. Under the optimized reaction conditions and in the presence of only 1 mol% **Q-2**, the desired products were obtained in 90% yield and with 88 : 12 dr and 95% ee (entry 18).

We next studied the scope of this direct Mannich reaction (Table 2). With 1 mol% **Q-2**, consistently high diastereoselectivities

Table 2 Reaction scope[a]

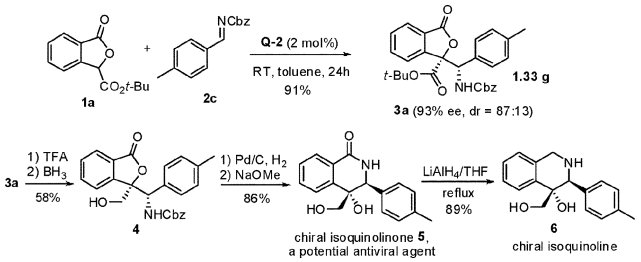


Entry	1	R^2	3	Yield[b]/%	dr[c]	ee[d]/%
1	**1a**	4-MeC_6H_4	**3a**	90	88 : 12	95
2	**1a**	4-OMeC_6H_4	**3b**	92	88 : 12	91
3[e,f]	**1a**	4-OMeC_6H_4	**3c**	81	91 : 9	92
4	**1a**	3-MeC_6H_4	**3d**	86	86 : 14	93
5	**1a**	Ph	**3e**	86	91 : 9	95
6[e,f]	**1a**	Ph	**3f**	83	92 : 8	91
7	**1a**	4-BrC_6H_4	**3g**	81	88 : 12	92
8	**1a**	3-BrC_6H_4	**3h**	80	83 : 17	91
9	**1a**	4-ClC_6H_4	**3i**	76	89 : 11	97
10[e,f]	**1a**	4-ClC_6H_4	**3j**	80	91 : 9	92
11	**1a**	4-FC_6H_4	**3k**	85	85 : 15	93
12	**1a**	2-FC_6H_4	**3l**	84	88 : 12	91
13[f]	**1a**	3,4-OMeC_6H_3	**3m**	93	92 : 8	85
14	**1a**	4-$CF_3C_6H_4$	**3n**	79	82 : 18	85
15[f]	**1a**	2-Furanyl	**3o**	71	67 : 33	80
16	**1a**	3-Furanyl	**3p**	86	73 : 27	83
17	**1d**	Ph	**3q**	92	86 : 14	91
18	**1d**	3-MeC_6H_4	**3r**	80	87 : 13	86
19	**1d**	4-ClC_6H_4	**3s**	93	84 : 16	93
20[e,f]	**1d**	4-ClC_6H_4	**3t**	79	88 : 12	87
21	**1d**	4-FC_6H_4	**3u**	90	85 : 15	91
22	**1d**	4-$CF_3C_6H_4$	**3v**	81	83 : 17	82
23	**1e**	Ph	**3w**	88	87 : 13	83
24[e,f]	**1a**	*i*-Bu	**3x**	82	70 : 30	62
25[e,f]	**1a**	*n*-Bu	**3y**	80	63 : 37	55

[a] Reactions were carried out using **1** (0.05 mmol), **2** (0.06 mmol), **Q-2** (0.005 mmol) in toluene (0.5 mL) at room temperature. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Determined by HPLC analysis on a chiral stationary phase. [e] *N*-Tosylimine was used. [f] With 5 mol% catalyst.

and very good enantioselectivities were observed for a wide range of aryl imines, regardless of the electronic nature and the substitution pattern of the aromatic ring (entries 1–16). In addition, the aromatic portion of phthalides could also be varied (entries 17–23). *N*-Tosylimines worked equally well, and comparable results were obtained. Alkyl imines could be employed with less satisfactory results (entries 24–25).

To demonstrate the value of our method in scaleable synthesis, we performed gram-scale synthesis of 3,3-disubstituted phthalides. The Mannich reaction between phthalide **1a** and Cbz imine **2c** proceeded smoothly in the presence of **Q-2**, affording gram-scale Mannich product **3a** in 91% yield, with 87 : 13 dr and 93% ee (Scheme 2). The Mannich products are valuable molecules due to the importance of 3,3-disubstituted phthalide substructures in natural products and medicinal chemistry.[5] Furthermore, such structures are versatile synthetic intermediates, and in particular, are valuable precursors to biologically important isoquinolinones and isoquinolines. As illustrated in Scheme 2, the *tert*-butyl ester in **3a** was selectively reduced to yield **4**, and the subsequent removal of the Cbz group and basic treatment resulted in smooth lactam formation to afford chiral isoquinolinone **5**, a potential antiviral agent against RNA viruses.[7] Further reduction with $LiAlH_4$ gave isoquinoline **6**, which represents another interesting structural motif in bioactive compounds.[8]



Scheme 2 Gram-scale direct Mannich reaction and preparation of isoquinolinones and isoquinolines.

The C–H bond at position 3 of the phthalide **1** is highly activated since it is a benzylic proton and is α-substituted with an oxygen and a carbonyl group, thus the C-3 proton is very acidic. From a mechanistic viewpoint, there are two possible pathways for this Mannich reaction: a vinylogous reaction[9] and a simple Lewis base activation.[10] The exact mechanism of the reaction has not been elucidated at this early stage, and we are carrying out further studies to understand the mechanism underlying this interesting transformation.

In conclusion, we have employed phthalide derivatives as donors in the direct asymmetric Mannich-type reaction for the first time; medicinally important and synthetically useful 3,3-disubstituted phthalides were prepared in excellent yields and with good diastereoselectivities and enantioselectivities in the presence of a quinine–*tert*-leucine trifunctional catalyst. The Mannich products were readily converted to chiral isoquinolinones and isoquinolines, both are synthetically and biologically significant molecular structures. Biological evaluations of the molecules prepared are underway, and we are also presently focusing on the extension of phthalides as donors in other asymmetric reactions.

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