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EDGE ARTICLE

Chiral phosphoric acid-catalysed Friedel–Crafts alkylation reaction of indoles with racemic spiro indolin-3-ones†

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Chiral phosphoric acid-catalysed Friedel–Crafts alkylation reactions of indoles, pyrrole and 3-(dimethylamino)phenol with racemic spiro indolin-3-ones have been realised. With 5 mol% (*S*)-TRIP, Friedel–Crafts adducts bearing a quaternary stereocentre were obtained in up to 99% yield and 99% ee. The reaction features readily available, stable starting materials and delivers synthetically useful but challenging products.

Construction of chiral quaternary carbon centres has been one of the most challenging subjects in asymmetric catalysis.[1] On the other hand, chiral quaternary carbon centers can be found extensively in natural products and unnatural compounds with intriguing properties. For instance, indol-3-yl methanamines possess quaternary carbon centres and are a very useful motif, exemplified by isatisine A (Fig. 1) and its acetonide derivative that display very interesting antiviral properties.[2,3] Retro-synthetically, indol-3-yl methanamines could be accessed directly from asymmetric Friedel–Crafts alkylation reactions.[4] However, despite enormous progress made with asymmetric Friedel–Crafts reactions during the past decade,[5] most of the Friedel–Crafts alkylation reactions of indoles with imines were limited to aldimine substrates.[6,7] There are very few examples of asymmetric Friedel–Crafts alkylation reactions of indoles with ketimines, which would lead to the synthesis of indol-3-yl methanamines bearing a quaternary carbon center.[8,9] In this regard, Zhou and co-workers developed an asymmetric Friedel–Crafts alkylation reaction of indoles with α-aryl enamides, which isomerized to ketimines *in situ*, catalysed by chiral phosphoric acids.[9] Chiral amine products bearing a quaternary carbon center were obtained in excellent ees but the substrates were limited to aryl methyl ketone derived enamides. In addition to the challenges faced in enantioselective control when using ketimines, their poor reactivity, stability and synthetic difficulty also impede progress toward asymmetric Friedel–Crafts alkylation reactions with ketimines. To address these problems, we recently envisaged that readily accessible racemic spiro indolin-3-ones might be suitable substrates in chiral phosphoric acid-catalysed Friedel–Crafts alkylation reaction.[10] Under acid catalysis, the racemic spiro indolin-3-ones with quaternary stereocentres undergo ring opening affording highly functionalised ketimines *in situ* (Scheme 1).[11] In this paper, we report our results on the novel asymmetric Friedel–Crafts alkylation reaction of indoles, pyrrole and 3-(dimethylamino)phenol with racemic spiro indolin-3-ones, affording highly enantioenriched Friedel–Crafts adducts bearing a quaternary carbon centre. Given the fact that both indolin-3-one and indole are privileged structural units in biologically active compounds,[12] the current methodology provides a facile access to novel scaffolds that would greatly benefit drug discovery research.

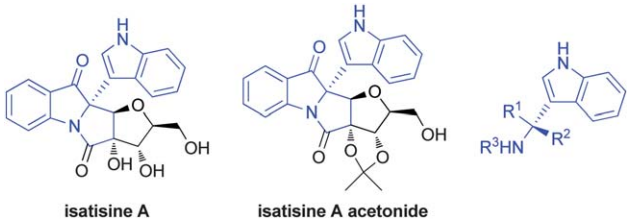
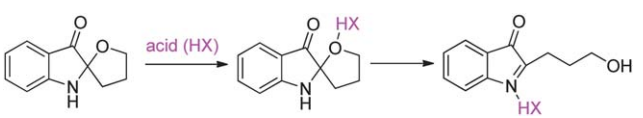


Fig. 1 Isatisine A, its acetonide derivative and indol-3-yl methanamines bearing a quaternary carbon center.

We first examined the reaction between spiro indolin-3-one **2a** and indole **3a** catalysed by different chiral phosphoric acids **1** (Table 1).[11] In the presence of 5 mol% (*S*)-TRIP (**1a**)[13] and 4 Å molecular sieves (MS) in dichloromethane at room temperature, reaction of **2a** with 2.0 equivalents of **3a** proceeded smoothly in



Scheme 1 Acid-catalysed *in situ* formation of ketimine from racemic spiro indolin-3-one.

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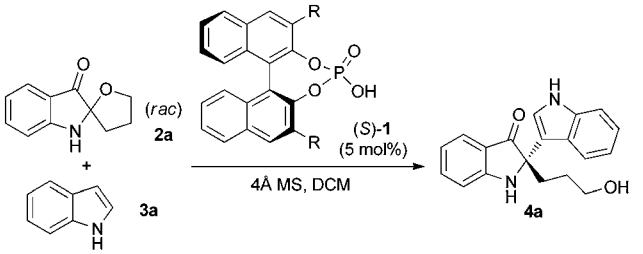
Table 1 Screening of different Brønsted acid catalysts and reaction temperatures

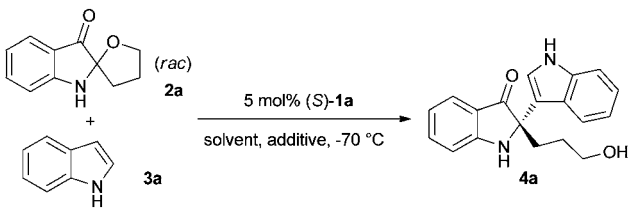


Entry[a]	1	R	*T*/°C	Yield[b] (%)	ee[c] (%)
1	**1a**	2,4,6-*i*Pr$_3$C$_6$H$_2$	rt	96	43
2	**1a**	2,4,6-*i*Pr$_3$C$_6$H$_2$	0	91	55
3	**1a**	2,4,6-*i*Pr$_3$C$_6$H$_2$	−40	92	91
4	**1a**	2,4,6-*i*Pr$_3$C$_6$H$_2$	−70	97	98
5	**1b**	4-*t*Bu-2,6-*i*Pr$_2$C$_6$H$_2$	−70	92	98
6	**1c**	4-NO$_2$C$_6$H$_4$	−70	90	75
7	**1d**	1-Naphthyl	−70	90	77
8	**1e**	Biphenyl	−70	94	5
9	**1f**	3,5-(CF$_3$)$_2$C$_6$H$_3$	−70	93	5
10	**1g**	SiPh$_3$	−70	92	80

[a] Reactions were performed with **2a** (0.1 mmol), indole **3a** (2 equiv.), 4 Å MS (10 mg) and 5 mol% of **1** in CH_2Cl_2. [b] Isolated yield. [c] Determined by HPLC.

complete conversion to afford the desired product **4a** in 43% ee (entry 1, Table 1). Lowering the reaction temperature significantly improved the enantioselectivity of this reaction, and the product was obtained in 98% ee at −70 °C (entry 4, Table 1). Various chiral phosphoric acids **1** were then tested at −70 °C (entries 5–10, Table 1). All the reactions went to completion with variable ees. Notably, catalyst **1b** (R = 4-*t*Bu-2,6-*i*Pr$_2$C$_6$H$_2$) also led to an excellent enantioselectivity comparable to catalyst **1a** (98% ee, entry 5, Table 1).

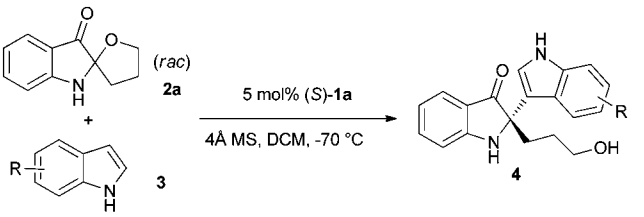
Table 2 Screening of different solvents and additives



Entry[a]	Solvent	Additive	*t*/h	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	4 Å MS	2	97	98
2	Toluene	4 Å MS	30	75	75
3	Diethyl ether	4 Å MS	48	Trace	—
4	Xylene	4 Å MS	30	75	41
5	CH_2Cl_2	—	15	88	97
6	CH_2Cl_2	3 Å MS	10	93	98
7	CH_2Cl_2	5 Å MS	4	90	98
8[d]	CH_2Cl_2	4 Å MS	25	88	98

[a] Reactions were performed with **2a** (0.1 mmol), indole **3a** (2 equiv.), additive (10 mg) and 5 mol% of **1a**. [b] Isolated yield. [c] Determined by HPLC. [d] Reaction was performed with 2 mol% **1a**.

Table 3 Asymmetric Friedel–Crafts reaction with various indoles



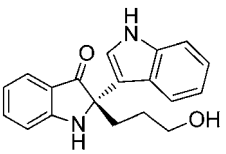
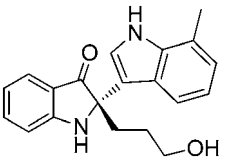
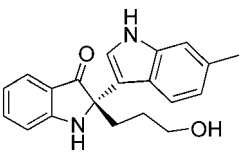
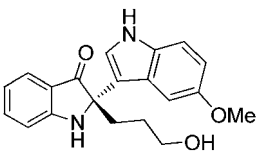
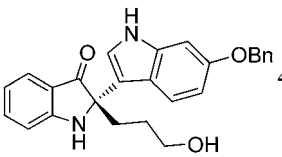
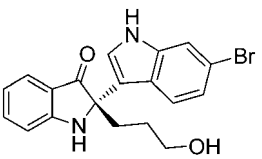
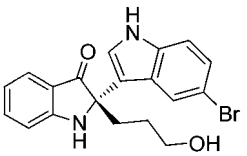
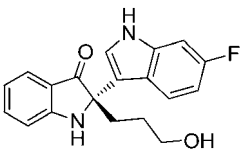
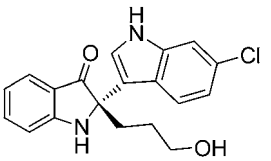
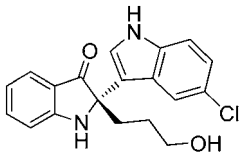
Entry[a]	Product	**4**, yield[b] (%)	ee[c] (%)
1		**4a**, 97	98
2		**4b**, 98	98
3		**4c**, 92	99
4		**4d**, 97	98
5		**4e**, 90	99
6		**4f**, 90	97
7		**4g**, 99	98
8		**4h**, 96	98
9		**4i**, 88	96

Table 3 (*Contd.*)

Entry[a]	Product	**4**, yield[b] (%)	ee[c] (%)
10		**4j**, 97	98

[a] Reactions were performed with **2a** (0.1 mmol), indole **3** (2 equiv.), 4 Å MS (10 mg) and 5 mol% of **1a**. [b] Isolated yield. [c] Determined by HPLC.

With (*S*)-TRIP (**1a**) as the catalyst, we further optimised the reaction conditions by tuning solvents (toluene, diethyl ether, and xylene), additives, and catalyst loadings, the results are summarised in Table 2. Overall, the reaction with 5 mol% (*S*)-TRIP and 4 Å MS in dichloromethane at −70 °C led to the best combination of isolated yield and enantioselectivity (97% yield, 98% ee, entry 1, Table 2).

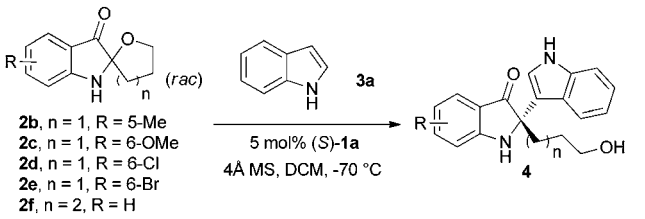
Under the above optimised reaction conditions, various substituted indoles were reacted with **2a** to probe the generality of the reaction. The results are summarised in Table 3. Several substituted indoles **3b–j**, containing either electron-donating (7-Me, 6-Me, 5-OMe, 6-OBn) or electron-withdrawing groups (6-Br, 5-Br, 6-F, 6-Cl, 5-Cl), were tested in the reaction with indolin-3-one **2a**. In all cases, excellent yields and enantioselectivities were achieved (88–99% yield, 96–99% ee, entries 2–10, Table 3).

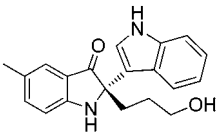
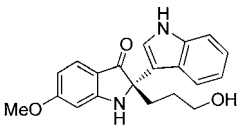
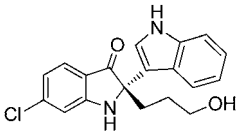
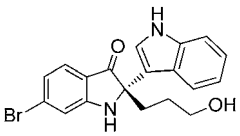
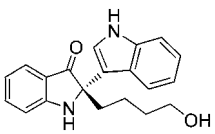
In addition, the reactions of various racemic indolin-3-ones bearing quaternary stereocentres with indole were also carried out to further examine the reaction scope. As summarised in Table 4, this asymmetric Friedel–Crafts reaction also works well for substituted indolin-3-ones. Excellent yields and enantioselectivities were obtained for indolin-3-ones bearing electron-donating groups (Me, OMe) (95–96% yield, 96–97% ee, entries 1 and 2, Table 4). When electron-withdrawing groups (Br, Cl) were introduced on the indolin-3-ones, the reactions proceeded with excellent yields but with slightly decreased enantioselectivities (92–95% yield, 88–89% ee, entries 3 and 4, Table 4). Six-membered ring containing substrate, 3′,4′,5′,6′-tetrahydrospiro[indoline-2,2′-pyran]-3-one **2f** (Table 4, $n = 2$) was tolerated in the reaction, giving the Friedel–Crafts adduct in 98% yield and 88% ee (entry 5, Table 4).

To further broaden the substrate scope for the Friedel–Crafts reaction with spiro indolin-3-ones, other types of electron-rich arenes such as pyrrole and 3-(dimethylamino)phenol were tested, as shown in Scheme 2. With pyrrole as the substrate, under slightly modified reaction conditions, the asymmetric Friedel–Crafts reaction of spiro indolin-3-ones **2a–b** led to the alkylation products **4p–q** in excellent yields and ees (R = H, 92% yield, 96% ee; R = Me, 90% yield, 97% ee, Scheme 2, eq 1). However, when 3-(dimethylamino)phenol was used, the reaction proceeded much more slowly, even at room temperature. The optimal enantioselectivity for product **4r** was obtained at only a moderate level (50% ee) in the presence of catalyst (*S*)-**1b** (Scheme 2, eq 2).

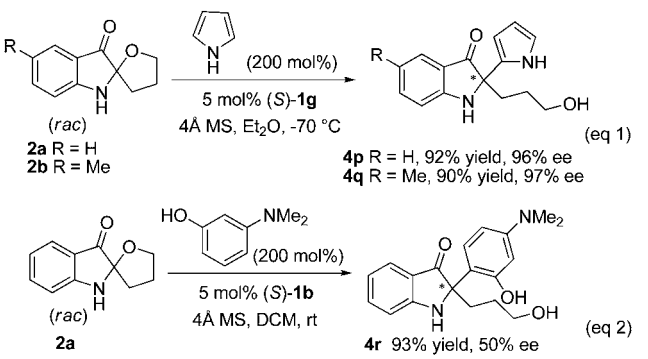
In order to determine the absolute configuration of the product, the crystal structure of enantiopure **4g** was obtained and a single-crystal X-ray analysis determined its configuration as *S* (Fig. 2).

Table 4 Asymmetric Friedel–Crafts reaction with substituted indolin-3-ones



Entry[a]	Product	**4**, yield[b] (%)	ee[c] (%)
1		**4k**, 95	96
2		**4l**, 96	97
3		**4m**, 92	89
4		**4n**, 95	88
5[d]		**4o**, 98	88

[a] Reactions were performed with **2** (0.1 mmol), indole **3a** (2 equiv.), 4 Å MS (10 mg) and 5 mol% of **1a**. [b] Isolated yields. [c] Determined by HPLC. [d] Reaction was carried out with 5 mol% of **1b**.



Scheme 2 Asymmetric Friedel–Crafts reaction with pyrrole and 3-(dimethylamino)phenol.

The products obtained here contain a free hydroxyl group that provides a versatile handle for performing subsequent transformations. Scheme 3 shows the synthetic utility of the products

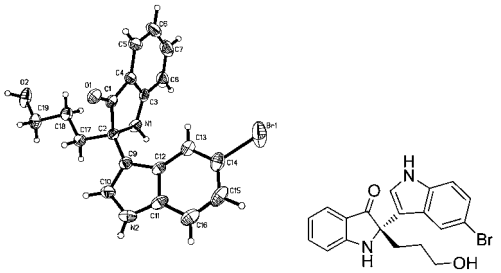
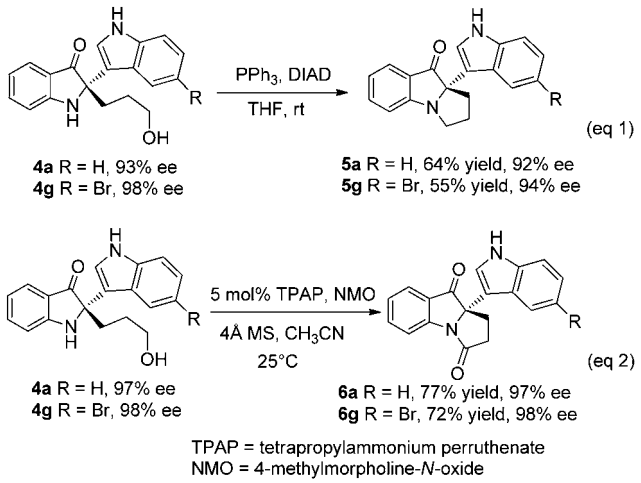


Fig. 2 X-Ray crystal structure of (*S*)-**4g**.



Scheme 3 Transformation of **4a** and **4g** to tricyclic compounds.

where treatment of **4a** (**4g**) with PPh_3/DIAD (diisopropyl azodicarboxylate) in THF delivers a dihydropyrrole ring yielding a tricycylic compound **5a** (**5g**) with good stereochemical integrity. Moreover, when product **4a** (**4g**) was subjected to Ley oxidation conditions,[14] tricycylic compound **6a** (**6g**) was formed in excellent ee. Notably, the latter tricyclic motif exists in isatisine A, thus potentially providing a basis for future asymmetric syntheses of isatisine A and related natural products.

In summary, we have developed an efficient method for the construction of chiral quaternary stereocentres by enantioselective Friedel–Crafts alkylation reaction of indoles, pyrrole and 3-(dimethylamino)phenol with racemic indolin-3-ones having quaternary stereocenters. With (*S*)-TRIP as the catalyst, Friedel–Crafts adducts bearing quaternary carbon centres were obtained in excellent yields and ees. The ready availability of indolin-3-ones as efficient ketimine precursors in this asymmetric reaction will greatly facilitate access to enantiopure amines bearing a quaternary carbon centre at the α-position. Further expansion of this reaction and application of the current methodology are underway in our laboratory.

Acknowledgements

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