Enantioselective Synthesis of Tetrahydropyrano[3,4-*b*]indoles Catalyzed by Chiral *N*-Triflyl Phosphoramide via Intramolecular Friedel–Crafts Alkylation Reaction

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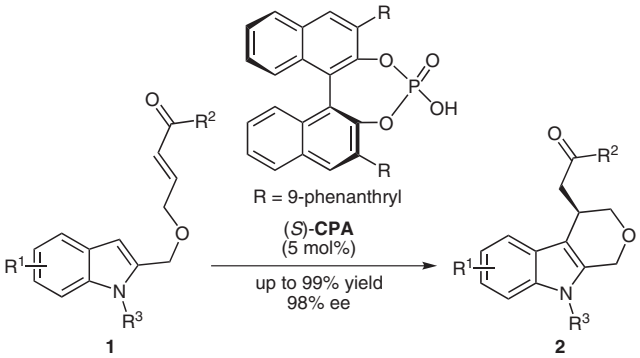
Abstract: A highly efficient intramolecular enantioselective Friedel–Crafts alkylation reaction of indolyl enones utilizing chiral *N*-triflyl phosphoramide catalyst is described. Various tetrahydropyrano[3,4-*b*]indoles (THPI) have been afforded with excellent yields and up to 98% ee.

Key words: asymmetric catalysis, chiral Brønsted acids, *N*-triflyl phosphoramide, Friedel–Crafts, indoles

Organocatalysts, which have been extensively developed in the last decade, are still of great research interest due to their inherent advantages such as robust, environmental benign, and cheap, but usually require high loading of the catalysts.[1] In the broad research field of organocatalysts, Brønsted acid is often classified as an important branch, which typically subdefined as H-bond donor catalysts such as thioureas[2] and stronger Brønsted acid catalysts (e.g., phosphoric acids).[3] Chiral *N*-triflyl phosphoramides derived from binaphthyl scaffold, since its first design and utilization in the asymmetric catalytic Diels–Alder reaction by Yamamoto and co-workers,[4] have attracted considerable attention due to their rigid chiral framework and even stronger acidity than chiral phosphoric acids.[5,6] Recently, chiral *N*-triflyl phosphoramides have been applied successfully in several asymmetric catalytic reactions by further broadening the activating mode and reaction scope.[4,5] In 2009, we reported an enantioselective construction of polycyclic indoles by a sequential catalysis of Ru-catalyzed olefin cross-metathesis and chiral phosphoric acid-catalyzed intramolecular Friedel–Crafts alkylation.[7–9] This asymmetric intermolecular Friedel–Crafts alkylation reaction catalyzed by 5 mol% of chiral phosphoric acid led to the facile construction of tetrahydropyrano[3,4-*b*]indoles in high enantioselectivities (Scheme 1).

As part of our ongoing program of developing highly efficient chiral Brønsted acid catalyzed asymmetric reactions,[10,11] we envisaged that the chiral *N*-triflyl phosphoramide, a stronger Brønsted acid than its corresponding phosphoric acid, might be a more efficient catalyst in the above intramolecular asymmetric Friedel–Crafts alkylation reaction. In this paper, we report the results from this study. Chiral *N*-triflyl phosphoramide was found an efficient catalyst for asymmetric intramolecular Friedel–Crafts alkylation reaction of indolyl enones, providing tetrahydropyrano[3,4-*b*]indoles in excellent yields and ee's. Notably, the catalyst loading could be as low as 1 mol%, and the ketone product could be readily transformed into an ester.



Scheme 1 Enantioselective construction of tetrahydropyrano[3,4-*b*]indoles by chiral phosphoric acid catalyzed intramolecular Friedel–Crafts alkylation

We began our study by examining various chiral phosphoramides in the cyclization reaction of **1a** in toluene at –20 °C. The data are summarized in Table 1. To our delight, all the phosphoramides, especially *N*-triflyl phosphoramides, proved to be efficient for this intramolecular Friedel–Crafts alkylation reaction, affording product **2a** in excellent yields within five minutes. This clearly indicates a better activation of the substrate by *N*-triflyl phosphoramides comparing with their corresponding phosphoric acids. Among these chiral *N*-triflyl phosphoramides, (*S*)-**3j** was the optimal one in terms of a combination of yield and ee (84% yield, 89% ee, Table 1, entry 10).

With the optimal catalyst (*S*)-**3j** in hand, reaction parameters including the reaction temperatures and solvents were then further optimized. As summarized in Table 2, the reaction at lower temperature proceeded smoothly with increased enantioselectivity but a longer reaction time (Table 2, entries 1–5). Reaction at –70 °C provided cyclization product **2a** in 97% yield and 95% ee (Table 2,

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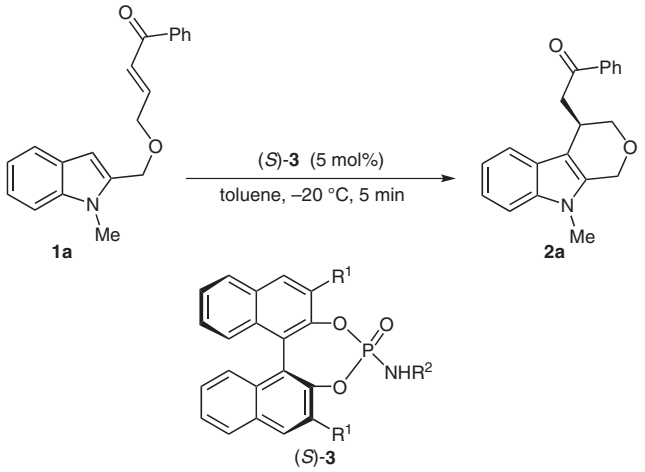
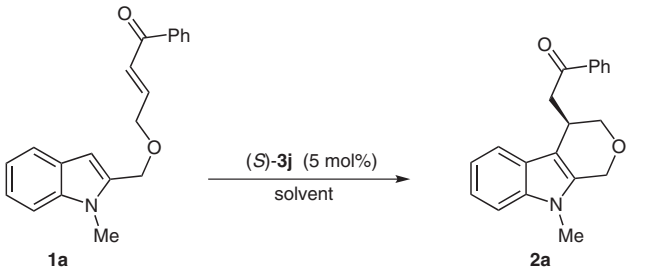
Table 1 Screening of Chiral Phosphoramides **3**[a]



Entry	**3** R^1, R^2	Yield (%)[b]	ee (%)[c]
1	**3a** H, $SO_2C_4F_9$	82	18
2	**3b** 3,5-$(CF_3)_2C_6H_3$, $SO_2C_8F_{17}$	88	62
3	**3c** 2,4,6-(*i*-Pr)$_3C_6H_2$, $SO_2C_8F_{17}$	95	30
4	**3d** 3,5-$(CF_3)_2C_6H_3$, Tf	99	67
5	**3e** 2,4,6-(*i*-Pr)$_3C_6H_2$, Tf	99	20
6	**3f** 3,5-$Me_2C_6H_3$, Tf	99	70
7	**3g** 4-biphenyl, Tf	97	50
8	**3h** 4′-[3,5-$(CF_3)_2$biphenyl], Tf	75	52
9	**3i** 4-$O_2NC_6H_4$, Tf	85	60
10	**3j** 9-anthryl, Tf	84	89
11	**3k** 9-phenanthryl, Tf	99	85
12	**3l** 4-pyrenyl, Tf	94	80
13	**3m** $SiPh_3$, Tf	91	75

[a] All the reactions were performed using **1a** (0.10 mmol) in 1 mL of toluene with 5 mol% of catalyst (*S*)-**3**.
[b] Isolated yield.
[c] Determined by HPLC analysis.

Table 2 Effects of Reaction Temperatures and Solvents[a]



Entry	Temp (°C)	Solvent	Time	Yield (%)[b]	ee (%)[c]
1	r.t.	toluene	<5 min	88	79
2	0	toluene	<5 min	99	85
3	–20	toluene	5 min	84	89
4	–40	toluene	5 min	90	92
5	–70	toluene	24 h	97	95
6	–40	CH_2Cl_2	5 min	99	88
7	–40	$CHCl_3$	8.5 h	99	78
8	–40	THF	3 h	18	57
9	–40	Et_2O	18 h	17	62
10	–40	MeCN	3 h	99	66
11	–40	hexane	13 h	78	12

[a] All the reactions were performed using **1a** (0.10 mmol) in 1 mL of solvent with 5 mol% of catalyst (*S*)-**3j**.
[b] Isolated yield.
[c] Determined by HPLC analysis.

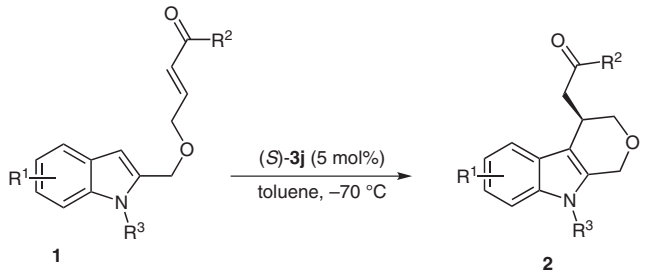
entry 5). Screening of various solvents such as toluene, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, acetonitrile, and hexane at –40 °C disclosed that toluene was the optimal one (Table 2, entries 4, 6–11). Notably, the reaction in dichloromethane gave a quantitative yield with slightly decreased enantioselectivity (88% ee, Table 2, entry 6).

Under the optimized reaction conditions (Table 2, entry 5), a wide range of substituted indolyl enones were investigated to test the generality of the reaction.

The results are summarized in Table 3. In general, all the tested substituted indolyl enones were smoothly converted into their corresponding cyclization products **2** with good to excellent yields. Substrates with either an electron-withdrawing group (Br, Cl) or an electron-donating group (OMe) at the 6-position of the indole core were all cyclized smoothly to provide THPI products with 92–98% ee (Table 3, entries 1–3). However, substituents (Br, Me) at the 5-position of the indole slightly lowered the enantioselectivities (Table 3, entries 4 and 5). When the N-protected group was switched from Me to Bn, the ee was maintained to be excellent for the cyclization product (83% yield, 95% ee, Table 3, entry 6). The indolyl enones with various substituted phenyl groups were also tested, and the cyclization products were obtained with good yields and ee (Table 3, entries 7–12). Interestingly, the substrate with a free OH group on the phenyl ring could be tolerated with a complete conversion (Table 3, entry 11). When an aliphatic ketone substrate **1n** (R^2 = Me) was tested, the intramolecular Friedel–Crafts alkylation reaction proceeded in 96% yield but with a low enantioselectivity (16% ee) (Table 3, entry 13). Quite remarkably, the reactions with reduced catalyst loadings (3 mol% and 1 mol%) at –70 °C worked also well without notable loss of yields and ee (Table 3, entries 14 and 15).

To broaden the application of this asymmetric synthetic methodology, transformation of the product **2b** into an ester was carried out, as shown in Scheme 2. Treatment of ketone **2b** with hydroxylamine afforded the oxime, which was subjected to the Beckmann rearrangement conditions

Table 3 Substrate Scope of the Intramolecular Friedel–Crafts Alkylation Reaction[a]



1 2

Entry	**1** R^1, R^2, R^3	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1b** 6-Br, Ph, Me	24	99	98
2	**1c** 6-Cl, Ph, Me	24	96	92
3	**1d** 6-MeO, Ph, Me	24	83	92
4	**1e** 5-Br, Ph, Me	42	81	63
5	**1f** 5-Me, Ph, Me	24	99	87
6	**1g** H, Ph, Bn	24	83	95
7	**1h** H, 4-$MeOC_6H_4$, Me	24	49	86
8	**1i** H, 4-ClC_6H_4, Me	24	94	96
9	**1j** H, 4-BrC_6H_4, Me	24	92	94
10	**1k** H, 4-MeC_6H_4, Me	24	99	97
11	**1l** H, 4-HOC_6H_4, Me	108	99	63
12	**1m** H, 2-naphthyl, Me	32	96	91
13	**1n** H, Me, Me	60	96	16
14[d]	**1b** 6-Br, Ph, Me	24	99	98
15[e]	**1b** 6-Br, Ph, Me	24	98	98

[a] All the reactions were performed using **1** (0.10 mmol) in 1 mL of toluene with 5 mol% of catalyst (*S*)-**3j** at –70 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Reaction was performed using 3 mol% of catalyst (*S*)-**3j**.
[e] Reaction was performed using 1 mol% of catalyst (*S*)-**3j**.

gave amide **4** in an overall 79% yield. Conversion of amide **4** into ester **5** was realized in a three-step manipulation. The ester **5** was obtained in an overall 65% yield with 98% ee. We believe the facile transformation of the ketone product without causing notable racemization of the chiral center will make the current synthetic methodology potentially useful in organic synthesis.

In conclusion, we found that chiral *N*-triflyl phosphoramide was an efficient catalyst for the asymmetric intramolecular Friedel–Crafts alkylation reaction of indolyl enones. With 1–5 mol% of the optimized catalyst, the substituted tetrahydropyrano[3,4-*b*]indoles were obtained in excellent yields and ee's. The transformation of the ketone moiety into an ester functionality was also successfully demonstrated.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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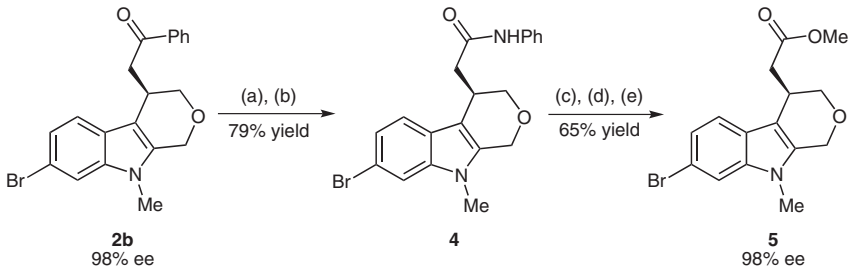

2b 98% ee **4** **5** 98% ee

Scheme 2 Conversion of ketone **2b** into ester **5**. (a) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, reflux; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, r.t., then MeCN, reflux; (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2; (d) LiOH, THF–H_2O (5:1); (e) $TMSCHN_2$, MeOH–benzene (1:1).

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