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Asymmetric Michael Addition of *N*-Boc-Protected Oxindoles to Nitroalkenes Catalyzed by a Chiral Secondary Amine

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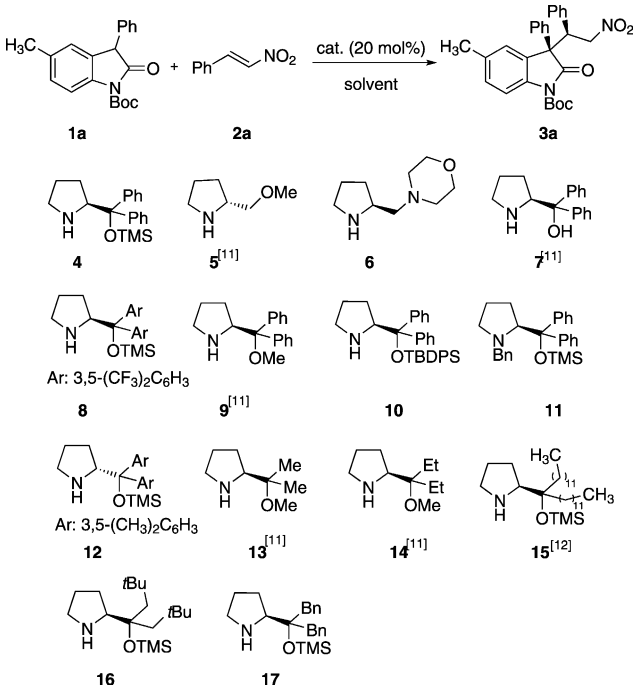
Over the last decade, chiral secondary amines have turned out to be very powerful catalysts for the efficient and highly stereoselective functionalizations of various carbonyl compounds through covalent activation modes such as iminium ion, enamine, and singly occupied molecular orbital (SOMO) activation.[1–4] Despite remarkable progress in this field, the substrate scope of these reactions is restricted to aldehydes and ketones thus limiting the applications of chiral secondary amines in catalysis. Although pyrrolidine is a common base used in organic synthesis, surprisingly, only very few efforts have been made to investigate its use as a chiral Brønsted base catalyst, whereas cinchona alkaloids and guanidines have attracted significant attention.[5] Furthermore, to the best of our knowledge, most of the developed reactions using secondary amines as H-acceptors employed chiral diaryl prolinols as bifunctional catalysts affording the products mostly in moderately good enantioselectivities.[6] We became interested in the possibility of developing highly diastereo- and enantioselective Michael additions using chiral secondary amines as Brønsted base catalysts.

The oxindole core exists as a characteristic structural feature in a large number of naturally occurring and synthetic alkaloids exhibiting various biological and pharmacological activities; of which, the most notable are its anti-tumor properties.[7] Therefore, many methods have been developed to approach 3,3-disubstituted oxindoles in a highly enantioselective manner.[8] Michael additions of oxindoles to nitroolefins are of particular interest as the Michael adducts can be readily converted to alkaloids or their derivatives.[9,10] Although several reports about Michael additions of N-protected oxindoles to nitroalkenes have been described, the catalysts used are either derived from expensive chiral precursors or synthesized through a long and challenging synthetic route.[9a–f] In this context we wish to report a Michael addition of oxindoles to nitroolefins catalyzed by a chiral pyrrolidine, which can be simply synthesized from the cheap amino acid proline (Scheme 1).



Scheme 1. Asymmetric Michael addition of **1a** to nitrostyrene **2a** employing pyrrolidine-type catalysts.

In the first instance we performed the reaction between the *N*-Boc-protected oxindole **1a** and nitrostyrene **2a** at room temperature in chloroform under the catalysis of (*S*)-diphenyl prolinol TMS-ether **4**. The reaction was complete within 2 h and gave the Michael adduct in a high yield (98%) and diastereomeric ratio (d.r. = 91:9), albeit with very low enantiomeric excess (*ee*) (3% *ee*; Table 1, entry 1). Lowering the reaction temperature to −35 °C led to an increase of the enantiomeric excess (27% *ee*), whereas the yield (98%) remained high (Table 1, entry 2). Then, several enantiopure secondary amines **5**–**8** were tested for this reaction. In the cases of (*R*)-2-methoxymethylpyrrolidine (**5**) and the diamine **6** the reactions proceeded in good to high yields (72–96%) and with excellent diastereoselectivities (d.r. = 97:3–99:1), however, no improved enantioselectivities (−6 to 12% *ee*) were obtained (Table 1, entries 3 and 4). When (*S*)-diphenyl prolinol **7** was used as catalyst, an inverse and higher enantioselectivity (−40% *ee*) was achieved but the catalytic activity diminished dramatically (Table 1, entry 5). In the case of (*S*)-diarylprolinol TMS-ether **8** the product

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Table 1. Optimization of the reaction conditions for the Michael addition.[a]

Entry	Cat.	T [°C]	t [h]	Solvent	Yield [%][b]	d.r.[c]	ee[c]
1	**4**	RT	2	$CHCl_3$	98	91:9	3
2	**4**	−35	16	$CHCl_3$	98	97:3	27
3	**5**	−35	16	$CHCl_3/CH_2Cl_2=4:1$	96	99:1	−6
4	**6**	−35	16	$CHCl_3/CH_2Cl_2=4:1$	72	97:3	12
5	**7**	−35	16	$CHCl_3/CH_2Cl_2=4:1$	46	87:13	−40
6	**8**	−35	16	$CHCl_3/CH_2Cl_2=4:1$	21	33:46	−6
7	**4**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	98	98:2	52
8	**4**	−60	24	EtOAc	82	95:5	18
9	**4**	−60	24	MeOH	<5	n.d.[d]	n.d.[d]
10	**4**	−60	24	ether	65	51:49	8
11	**4**	−60	24	THF	74	66:34	19
12	**4**	−60	24	toluene	78	65:35	19
13	**9**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	97	>99:1	51
14	**10**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	98	93:7	32
15	**11**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	<5	51:49	2
16	**12**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	96	>99:1	−63
17	**13**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	98	99:1	70
18	**14**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	98	>99:1	77
19	**15**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	98	>99:1	83
20	**16**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	96	95:5	29
21	**17**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	94	>99:1	26
22[e]	**15**	−60	24	$CHCl_3/CH_2Cl_2=4:1$	98	>99:1	83

[a] The reactions were performed on a 0.25 mmol scale of *N*-Boc-protected oxindole **1a** using nitrostyrene **2a** (1.2 equiv) and catalyst (20 mol%) in solvent (5.0 mL). [b] Yields of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Not determined. [e] Carried out with 10 mol% catalyst.

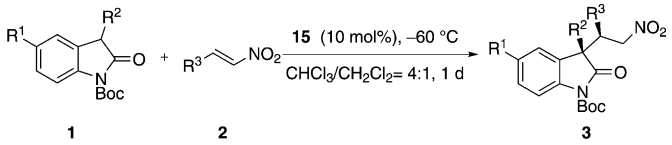
was obtained in a low yield (21%) and with inverse stereoselectivities (d.r.=33:46, −6% *ee*), indicating that the feature of the aromatic ring of the catalyst showed influence on both its catalytic activity and selectivity (Table 1, entry 6). To improve the enantioselectivity we conducted the reaction at −60°C in a mixture of chloroform/dichloromethane (4:1), which gave the product after 24 h in higher stereoselectivities (d.r.=98:2, 52% *ee*) without decrease of the yield (98%; Table 1, entry 7). Next, a brief solvent screening was undertaken at −60°C by using (*S*)-diphenyl prolinol TMS-ether **4** as catalyst. Unfortunately, no improved enantioselectivity was acquired. In the case of ethyl acetate as solvent the product was obtained in a high yield (82%) and diastereoselectivity (d.r.=95:5), whereas the reaction in methanol was nearly shut down (Table 1, entries 8 and 9). In the other solvents both the diastereomeric ratios and enantiomeric excesses decreased to a low level (d.r.=66:34–51:49, 8–19% *ee*; Table 1, entries 10–12).

Subsequently, we investigated how the substituents on the catalyst influence the outcome of this reaction. At first we varied the protective group of the alcohol moiety of the catalyst. In the case of the catalyst **9** bearing a less bulky methoxy group, an almost identical result was obtained (97%, d.r.>99:1, 51% *ee*) in comparison to its TMS analogue (Table 1, entry 13). Employing the more sterically demanding (*S*)-diphenyl prolinol TBDPS-ether **10** as catalyst resulted in a drop of both diastereo- and enantioselectivity (d.r.=93:7, 32% *ee*; Table 1, entry 14). In the next instance the reaction was carried out under the catalysis of benzyl-protected (*S*)-diphenyl prolinol TMS-ether **11**. In this case only traces of product were formed indicating that the secondary amine group plays a crucial role in the activation of the substrate (Table 1, entry 15). Furthermore, we screened various diaryl and dialkyl prolinol ethers **12**–**17** for this reaction. The catalyst **12** with a larger aryl ring was found to improve the enantioselectivity (−63% *ee*) to some degree (Table 1, entry 16). Surprisingly, when the less sterically demanding (*R*)-2-methoxymethylpyrrolidine **13** was employed as catalyst, the product was furnished in a better enantioselectivity (70% *ee*; Table 1, entry 17). Encouraged by this result we carried out this reaction with several other dialkyl prolinol ethers **14**–**16** (Table 1, entries 18–20) and the best result with respect to both yield (98%) and stereoselectivities (d.r.>99:1, 83% *ee*) was obtained when (*S*)-didodecyl prolinol TMS-ether **15** was utilized as the catalyst (Table 1, entry 19). Moreover, (*S*)-dibenzyl TMS-prolinol ether **17** was tested for this reaction providing no improved result (Table 1, entry 21). Finally, we lowered the catalyst loading of **15** to 10 mol% and the reaction was complete within 24 h affording the product in excellent yield (98%), diastereoselectivity (d.r.>99:1), and high enantioselectivity (83% *ee*; Table 1, entry 22).

After optimizing the reaction conditions we started to evaluate the substrate scope of this reaction by varying the structure of both *N*-Boc-protected oxindoles **1** and nitroolefins **2**. Generally, all the reactions were completed within 24 h at −60°C under the catalysis of TMS-didodecyl prolinol ether **15** affording the products consistently in high to excellent yields (88–98%) and excellent diastereoselectivities (d.r. 98:2–>99:1; Table 2). In the case of 3-aryloxindoles, the substituents at the C5 position of the indole ring appeared to influence the level of stereoselectivities. When the oxindole **1a**,**b** were used as precursors, the products **3a**–**c** were obtained with good enantioselectivities (82–84% *ee*), whereas in the case of 5-methoxy-3-phenyl oxindole **1c**, the reaction afforded the product **3d** with virtually complete asymmetric induction (>99% *ee*). When 3-benzyl oxindoles **1d**–**h** were reacted as nucleophiles with various aromatic and heteroaromatic nitroalkenes **2a**–**d**, the reactions proceeded well and provided the products **3e**–**l** in excellent diastereo- and enantioselectivities (d.r.=98:2–>99:1, 91–97% *ee*). Moreover, 3-methyl oxindole **1i** was also found to be an active precursor for the Michael addition to nitrostyrene **2a** furnishing the product **3m** in a high yield (88%), excellent diastereomeric ratio (d.r.>99:1) and good enantiomeric excess (83% *ee*). A limitation of this reaction was observed in the case of aliphatic nitroolefin **2e**, which did not react with the oxindole **1d** even at room temperature.

The relative and absolute configuration of **3e** and **3m** was assigned to be *S* for the quaternary center and *R* for the tertiary center by comparing their NMR spectra and optical rotations with the corresponding analyses reported in the literature.[13] The configuration of the other products was deduced assuming a uniform reaction pathway.

Table 2. Yields and stereoselectivities of the Michael addition of *N*-Boc oxindoles **1** to nitroalkenes **2**.[a]



1 **2** **3**

1a: R^1= CH_3, R^2= Ph;
1b: R^1= H, R^2= Ph;
1c: R^1= OCH_3, R^2= Ph;
1d: R^1=H, R^2= Bn;
1e: R^1= H, R^2= *m*-$FC_6H_4CH_2$;
1f: R^1= H, R^2= *p*-$MeOC_6H_4CH_2$;
1g: R^1= H, R^2= *p*-$CH_3C_6H_4CH_2$;
1h: R^1= H, R^2= piperonylmethyl.

2a: R^3 = Ph;
2b: R^3 = 2-furyl;
2c: R^3 = *p*-$CH_3C_6H_4$;
2d: R^3 = *p*-FC_6H_4;
2e: R^3= *n*Pr.

3	R^1	R^2	R^3	Yield [%][b]	d.r.[c]	*ee* [%][c]
a	CH_3	Ph	Ph	98	>99:1	83
b	CH_3	Ph	2-furyl	98	98:2	84
c	H	Ph	Ph	96	>99:1	82
d	OCH_3	Ph	*p*-$CH_3C_6H_4$	97	>99:1	>99
e	H	Bn	Ph	98	>99:1	97
e[d]	H	Bn	Ph	98	>99:1	97
f	H	Bn	*p*-FC_6H_4	91	>98:2[e]	97
g	H	Bn	*p*-$CH_3C_6H_4$	92	>98:2[e]	91
h	H	Bn	2-furyl	95	98:2	94
i	H	*m*-$FC_6H_4CH_2$	Ph	98	98:2	92
j	H	*p*-$MeOC_6H_4CH_2$	Ph	98	99:1	92
k	H	*p*-$CH_3C_6H_4CH_2$	Ph	98	99:1	92
l	H	piperonylmethyl	Ph	97	99:1	91
m	H	Me	Ph	88	>99:1	83
n	H	Bn	*n*Pr	0	–	–

[a] The reactions were performed on a 0.25 mmol scale of *N*-Boc-protected oxindoles **1** using nitroalkenes **2** (1.2 equiv) and catalyst **15** (10 mol%) in a mixture of chloroform/dichloromethane (4:1; 5.0 mL). [b] Yields of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Carried out on a 1 mmol scale. [e] d.r. of isolated product determined by using ^{1}H NMR spectroscopy.

A proposed transition state of this reaction is illustrated in Figure 1, in which the pyrrolidine catalyst activates both the oxindole in its enol form and the nitro group of the Michael acceptor through hydrogen bonds. The *Re* face of the prochiral C_α of the oxindole is shielded by the bulky side chain of the catalyst so that the nitroalkene approaches the oxindole favorably from its *Si* face.

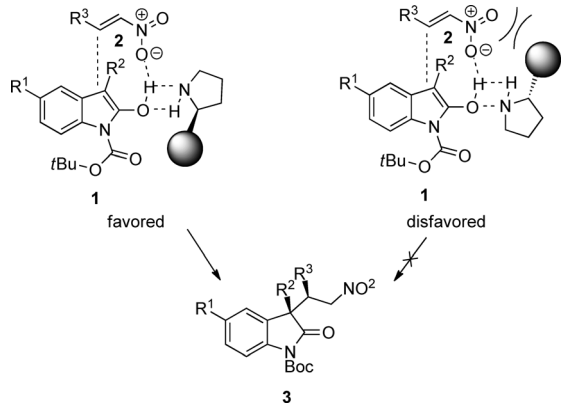
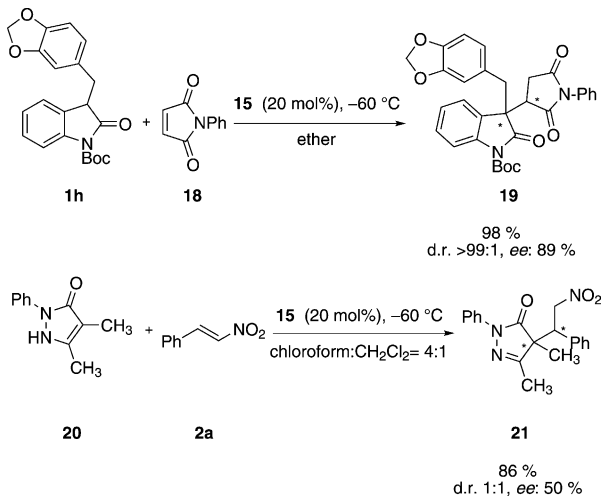


Figure 1. Proposed favored transition state of the Michael addition of *N*-Boc-protected oxindoles **1** to nitroalkenes **2**.

Furthermore, we have also investigated the application of the pyrrolidine catalyst **15** in other Michael additions. Two examples were shown in Scheme 2. In the case of *N*-phenyl maleimide **18** as the Michael acceptor and the oxindole **1h** as the nucleophile, the reaction proceeded well at −60 °C affording the product **19** in an excellent yield (98%), diastereomeric ratio (d.r.> 99:1) and high enantioselectivity (89% *ee*). Additionally, the Michael addition involving pyrazinone **20** and nitrostyrene **2a** could also be efficiently catalyzed by the didodecyl prolinol TMS-ether **15** giving the adduct **21** in a high yield (86%) and moderate enantioselectivity (50% *ee*).



Scheme 2. Michael additions catalyzed by didodecyl prolinol TMS-ether **15**.

In summary, we have developed a secondary amine-catalyzed asymmetric Michael addition of *N*-Boc-protected oxindoles to nitroolefins. This process was efficiently promoted by didodecyl prolinol TMS-ether through a Brønsted base activation mode furnishing the products in excellent yields (88–98%), diastereoselectivities (d.r. = 98:2–>99:1), and with high to excellent enantioselectivities (82–>99% *ee*). Remarkably, this catalyst was found to be active in other Michael additions, which will be reported in due course. Furthermore, applications of the Brønsted base activation mode of secondary amines with other nucleophile and electrophile combinations are also ongoing in our laboratories.

Experimental Section

General procedure for the Michael addition of *N*-Boc oxindoles to nitroolefins: Nitroolefins **2** (0.30 mmol) were added to a solution of 3-substituted *N*-Boc oxindoles **1** (0.25 mmol) and didodecyl prolinol TMS-ether **15** (10 mol%) in a mixture of chloroform/dichloromethane (4:1; 5 mL) at −60 °C. After stirring for 24 h the solvent was removed in vacuum and the residue was purified by flash column chromatography on silica gel

(*n*-pentane/ethyl acetate) affording the corresponding 3,3-disubstituted *N*-Boc oxindoles **3** as a colorless syrup.

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Keywords: asymmetric synthesis · Brønsted bases · Michael addition · organocatalysis · oxindoles

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