J|A|C|S COMMUNICATIONS

Published on Web 06/05/2009

Thiourea-Catalyzed Highly Enantio- and Diastereoselective Additions of Oxindoles to Nitroolefins: Application to the Formal Synthesis of (+)-Physostigmine

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Oxindoles are important building blocks found in many pharmaceuticals and in alkaloid natural products.[1] Most catalytic methods for the synthesis of these compounds require the use of transition metals.[2−6] Alternative catalytic procedures include asymmetric alkylation of oxindoles and the asymmetric Black rearrangement reaction of indolyl carbonates; the former has limited success.[7,8] We envisioned the nucleophilic addition of oxindoles to nitroolefins as an alternative organocatalytic method for the synthesis of these structural motifs (Figure 1). This approach may provide access to a wide range of spiral oxindoles or indoline derivatives bearing a quaternary center at the C3 position.

Over the past several years, numerous reports on thiourea-catalyzed asymmetric C−C bond-forming reactions have been published.[9] The carbon nucleophiles employed in these reactions include cyanide, indole derivatives, silyl ketene acetals, enamines, and stable enolates derived from 1,3-carbonyl compounds.[10−14] In contrast, the use of oxindoles as nucleophiles in the analogous transformation has been limited.[15−17] Herein, we report the first examples of thiourea-catalyzed, highly enantio- and diastereoselective additions of oxindoles to nitroolefins and the application of this methodology to the formal synthesis of (+)-physostigmine.

There were challenges associated with the proposed 1,4-addition reaction. One was the creation of a chiral quaternary center at C3, which is sterically congested, as the Michael reaction is generally sensitive to sterics.[18] Another was control of both the relative and absolute configurations of the two newly created stereogenic centers. It was not clear whether catalysts that imparted chirality to the oxindole or nitroolefin alone or to both would be required in order to achieve high asymmetric induction.

The addition of oxindole **1a** to nitrostyrene **2a** in the presence of catalyst **3a** (10 mol %) (Chart 1) was examined (Table 1).[19,20] Gratifyingly, the desired product **4a** was obtained in good yield and good diastereomeric ratio (dr), albeit with low enantiomeric excess (ee) (entry 1). A variant of **3a** was also tested, but the results were unsatisfactory (entry 2). It appeared that thiourea catalysts having cinchona alkaloid scaffolds did not effectively provide good asymmetric induction. Thus, cyclohexane-derived thiourea catalysts **3c** and **3d** (Chart 1) were explored.[21,22] These catalysts were expected to activate solely nitroolefins by H-bonding and were used in combination with an external base to promote the reaction. Unfortunately, **4a** was obtained with low to moderate ee (entries 3 and 4). These results suggested that activation of both the oxindole and nitroolefin was necessary for high selectivity. For this reason, catalyst **3e** was employed in the 1,4-addition reaction.[23] With this catalyst, a significant improvement in ee was observed (entry 5). Moreover, no external base was required for the reaction to proceed, indicative of the bifunctional nature of **3e** (entry 5 vs 6). Slight differences in dr and ee were observed in these cases, suggesting the structure of the base had an effect on these two parameters. This led to the design of catalyst **3f**, which proved most effective. A subsequent solvent screen resulted in selection of conditions that significantly increased the ee without diminishing the yield and dr (entries 7−10). These results are consistent with previous reports that nonpolar solvents without Lewis basic sites are generally optimal in conjunction with these types of thiourea catalysts.[23] Finally, with newly synthesized catalyst **3f**, product **4a** was obtained in excellent yield, dr, and ee (entries 11 and 12 vs 10).[24]

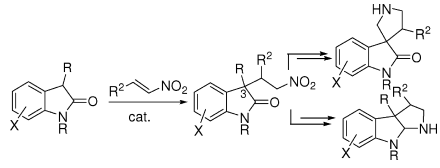
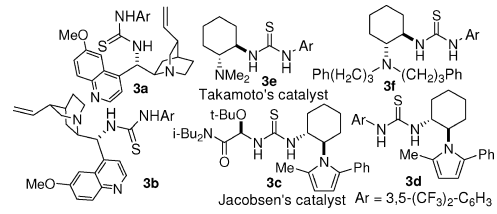


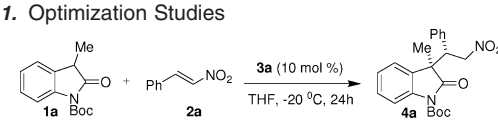
Figure 1. Synthetic route to oxindole derivatives.

Chart 1



Next, the scope of the 1,4-addition reaction with respect to both the nucleophile and electrophile was investigated (Table 2). Oxindole products bearing various substituents at C3 were obtained in good yields with good to excellent dr and ee (entries 1−5). A slight variation in dr was observed. Various electron-rich and -poor nitrostyrene derivatives with different substitution patterns on the aromatic ring were also examined (entries 6−10). High dr and ee were obtained in

Table 1. Optimization Studies

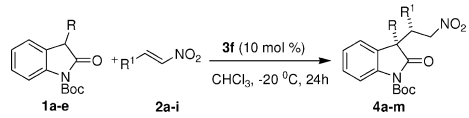


entry	catalyst	solvent	yield (%)[a]	dr[b]	ee (%)[c]
1	**3a**	THF	82	10:1	31
2	**3b**	THF	57	5:1	5
3[d]	**3c**	THF	88	5:1	60
4[d]	**3d**	THF	80	2:1	2
5[d]	**3e**	THF	87	6:1	74
6	**3e**	THF	84	4:1	78
7	**3e**	xylene	80	7:1	89
8	**3e**	toluene	77	5:1	87
9	**3e**	CH_2Cl_2	95	6:1	93
10	**3e**	$CHCl_3$	87	5:1	95
11	**3f**	$CHCl_3$	96	10:1	99
12	**3f**	CH_2Cl_2	91	9:1	92

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral-phase HPLC analysis. [d] Reaction run in the presence of 1 equiv of Hunig's base.

10.1021/ja903520c CCC: $40.75

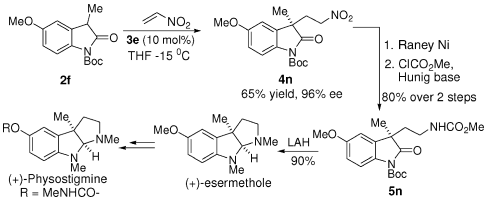
Table 2. Addition of Oxindoles to Nitroolefins



entry	R	R^1	product	yield (%)[a]	dr[b]	ee (%)[c]
1	Me	Ph	**4a**	96	10:1	99
2	Et	Ph	**4b**	95	5:1	96
3	allyl	Ph	**4c**	89	6:1	94
4	cinamyl	Ph	**4d**	90	11:1	92
5	4-Br-Bn	Ph	**4e**	86	5:1	88
6	allyl	4-Br-C_6H_4	**4f**	92	6:1	91
7	allyl	3-Br-C_6H_4	**4g**	91	9:1	95
8	allyl	4-MeO-C_6H_4	**4h**	91	5:1	90
9	allyl	4-OH-C_6H_4	**4i**	92	7:1	92
10	allyl	3,4-Cl_2-C_6H_3	**4j**	72	3:1	89
11	allyl	2-furyl	**4k**	97	6:1	99
12	allyl	n-C_7H_{15}	**4l**	95	>20:1	94
13	allyl	$(MeO)_2CH$	**4m**	68	>20:1	93

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral-phase HPLC analysis.

Scheme 1



most of these cases. Heteroaromatic nitroolefins were also viable substrates (entry 11). More interestingly, the addition reaction of aliphatic nitroolefins proceeded smoothly to afford products **4l** and **4m** in moderate to good yields with high dr and ee (entries 12−13). Both relative and absolute configurations at the two newly created centers were established by X-ray dispersion analysis of a sulfonamide derived from product **4a**.[25] The configuration of the stereogenic center at C3 was *R* and that at the remaining stereocenter was *S*. These data indicated that compound **4n** might be further elaborated to give (+)-esermethole, which is a known intermediate in the synthesis of (+)-physostigmine.[26]

To illustrate the synthetic utility of this methodology and further confirm the absolute stereochemistry of this reaction, we undertook the formal synthesis of (+)-physostigmine. The addition of oxindole **2f** to nitroethylene in the presence of catalyst **3e** (10 mol %) afforded product **4n** with 83% ee (Scheme 1).[27−29] A single recrystallization provided **4n** with 96% ee. Raney nickel reduction of this compound followed by methyl carbamate formation provided the key intermediate **5n**, which underwent reductive cyclization to afford (+)-esermethole in 72% overall yield over three steps.[30]

In summary, we have demonstrated a novel organocatalytic approach to the synthesis of pyrrolidinoindolines using 1,4-addition of oxindole derivatives to nitroolefins as a key step. The addition reaction was general with respect to oxindoles and nitroolefins and provided the desired products bearing a chiral quaternary center at C3 in good yield with good to excellent dr and ee. These features make this method synthetically viable and attractive, as illustrated in the formal synthesis of (+)-physostigmine. Further investigations of the scope and synthetic utility of this chemistry are underway, and the results will be reported in due course.

Acknowledgment. This research was supported by The Skaggs Institute for Chemical Biology.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, and a transition state proposal. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) With **3f**, the reaction stalled, perhaps because of catalyst poisoning or the polymerization of nitroethylene. **3e** provided similar ee's when the reaction was performed between−15 and−20 °C; the former gave a slightly better yield. THF was used instead of chloroform because of the solubility characteristics of **2f**.
(29) With the *N*-methyl protecting group, there was no reaction. We believe the Boc protecting group enhanced the acidity of the methine proton, thereby allowing the enolization of **2f** to be more facile.
(30) The absolute configuration of (+)-esermethole was determined by comparing the optical rotation of the synthesized material with the literature value.

JA903520C