

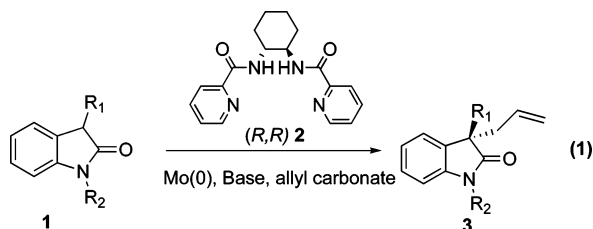
## Molybdenum-Catalyzed Asymmetric Allylation of 3-Alkylloxindoles: Application to the Formal Total Synthesis of (–)-Physostigmine

Barry M. Trost\* and Yong Zhang

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received January 24, 2006; E-mail: bmtrout@stanford.edu

The 3,3'-dialkyl oxindoles are ubiquitous in nature and have been shown to be valuable building blocks for alkaloid synthesis.<sup>1</sup> However, only a few methods exist for the direct asymmetric synthesis of such a structural motif due to the difficulty of constructing all-carbon quaternary stereocenters.<sup>2</sup> Recently, our group has demonstrated the palladium-catalyzed asymmetric allylic alkylation (AAA reaction) of prochiral nucleophiles to be an effective strategy for the generation of quaternary stereocenters, giving excellent yields and enantioselectivities for  $\beta$ -ketoesters,<sup>3a</sup> ketones,<sup>3b-c</sup> and 3-aryl oxindoles.<sup>3d</sup> However, when the Pd-catalyzed AAA reaction was applied to 3-alkyl oxindoles, only modest enantioselectivity was obtained despite numerous optimizations. Therefore, we turned our attention to the molybdenum-catalyzed AAA reaction, which has been demonstrated to proceed with excellent regio-, enantio-, and diastereoselectivities when unsymmetrical allyl carbonates were used as electrophiles.<sup>4</sup> The mechanism of the Mo-catalyzed AAA reaction involves nucleophiles pre-coordinating to the metal followed by reductive elimination and hence is distinctively different from that of the palladium process, which proceeds via direct attack of the nucleophiles on the  $\pi$ -allyl from the face opposite palladium.<sup>5</sup> The intimate interaction between the nucleophiles and the chiral metal catalyst in the molybdenum system led us to postulate the possibility of reacting prochiral nucleophiles with symmetrical allyl carbonate to generate quaternary stereocenters. Herein, we report the first examples of molybdenum-catalyzed enantioselective allylation of any prochiral nucleophiles (eq 1) and the application of this method to the formal synthesis of (–)-physostigmine and its analogues.<sup>6</sup>

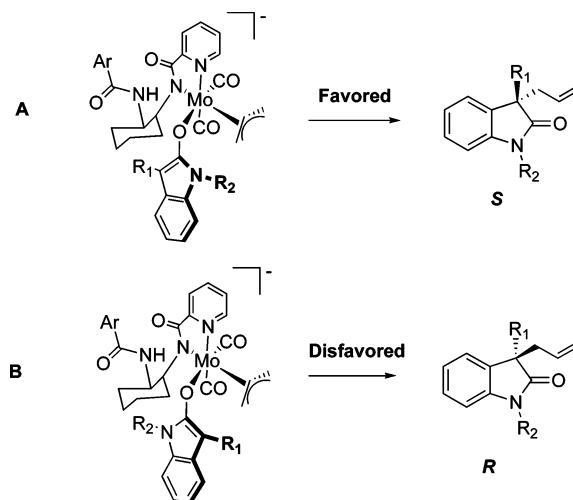


Optimization of the ligand, solvent, and base revealed that the counteraction of the base had the largest effect on the enantioselectivity of the reaction (Table 1). Bases with lithium as counterion provided the highest enantioselectivity (entries 3–9). Addition of 1 equiv of LiO*t*Bu and 1 equiv of LiHMDS (entry 6), or simply 2 equiv of LiO*t*Bu (entry 7), afforded the best conversion.<sup>7</sup> Running the reaction at room temperature or 4 °C gave comparable enantioselectivity and yields; lowering the temperature further lowers the ee. Thus, the use of Mo(C<sub>7</sub>H<sub>8</sub>)(CO)<sub>3</sub> (10% mol), ligand **2** (15% mol), and LiO*t*Bu (2 equiv) in THF at room temperature became our standard conditions for the synthesis of allylated 3-alkyl oxindoles.

**Table 1.** Selected Optimization Studies for Oxindole **4**<sup>a</sup>

entry	base	temperature	ee (%) <sup>b</sup>	yield (%) <sup>c</sup>
1	KHMDS	67 °C	38	–
2	NaHMDS	67 °C	60	–
3	LiHMDS	67 °C	75–78	75–92
4	<i>s</i> -BuLi	67 °C	71	–
5	LiHMDS	rt	80	45(94) <sup>d</sup>
6	LiHMDS/LiO <i>t</i> Bu	rt	81	95
7	LiHMDS (2 equiv)	rt	–	trace
8	LiO <i>t</i> Bu (2 equiv)	rt	80–82	95–98
9	LiO <i>t</i> Bu (2 equiv)	4 °C	82	95
10	LiO <i>t</i> Bu (2 equiv)	–10 °C	73	90

<sup>a</sup> Reaction performed with Mo(C<sub>7</sub>H<sub>8</sub>)(CO)<sub>3</sub> (10% mol), ligand **2** (15% mol), and oxindoles/allyl *tert*-butyl carbonate/base (1/1.2/1) at 0.1 M in THF. <sup>b</sup> Determined by chiral HPLC. <sup>c</sup> Isolated yields of allylated oxindoles. <sup>d</sup> Based on recovered starting material.



**Figure 1.** Model for enantiodiscrimination.

After establishing the optimized conditions, the scope and limitation of the reaction was examined (Table 2). In nearly all cases, excellent yields and good-to-excellent enantioselectivity were obtained. Substitution on the oxindole ring does not affect the reaction (entry 1). A large variety of functionalities at the three positions of the oxindoles are tolerated. Increasing the size of the 3-alkyl group increased the ee (entries 2, 4, and 8, entries 14 and 16). However, increasing the size of the N-protecting group was detrimental to the enantioselectivity (entries 2–3, 4–7, 8–9, and 14–16). This is not unexpected as the oxindole enolate is likely coordinated to the bulky molybdenum catalyst during the reaction and would try to minimize steric interactions by steering the large substituent away from the catalyst. The alkylation reaction is also highly chemoselective. No  $\alpha$ -alkylation of a nitrile (entries 10 and 11) or N-alkylation of a Boc-protected aniline (entry 12) was observed despite the fact that 2 equiv of base was used.

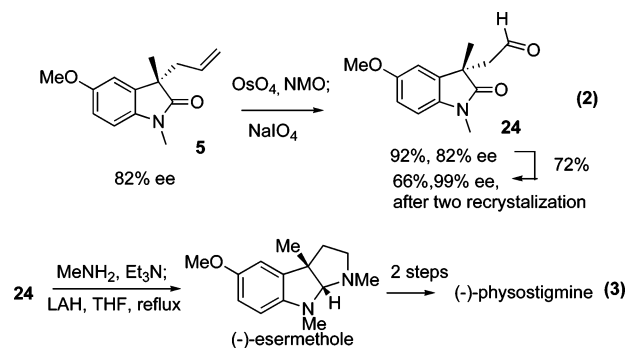
**Table 2.** Scope of Mo-catalyzed AAA for 3-Alkyl Oxindoles

entry	substrate	product	R	ee(%)	yield(%)
1				82	98
2			R=Me	81	99
3			R=Bn	75	93
4			R=Me	93	95
5			R=MOM	87	95
6			R=Bn	87	92
7			R=allyl	88	99
8			R=Me	91	96
9			R=Bn	85	98
10			R=Me	93	99
11			R=allyl	93	98
12				95	96
13				80	95
14			R=Me	80	95
15			R=MOM	75	96
16			R=Bn	74	98
17				88	96
18				75	94

The absolute stereochemistry of **5** was established by oxidation of the allyl group to its corresponding aldehyde (eq 2) and comparison of its optical rotation with the known enantiomer.<sup>1b</sup> The stereochemistry of the remaining examples are then assumed by analogy. The selectivity is in agreement with the transition state depicted in Figure 1. The facial approach in A is favored because it lessens the steric congestion between the ligand and the enolate of the oxindole as the C-terminus of the enolate moves toward the  $\pi$ -allyl. In the alternative approach in B, the steric interaction becomes more severe as the bulk of the oxindole is pushed toward the ligand during the bond formation. One or more lithium cations are likely also present to help organize and rigidify the chiral pocket and hence enhance the enantioselectivity of the reaction.

The utility of the Mo-catalyzed AAA of 3-alkyl oxindoles is demonstrated by a formal total synthesis of (-)-physostigmine, a

powerful inhibitor of acetyl cholinesterase (eqs 2–3).



The oxindole **4** is readily available in two steps from 4-methoxy-*N*-methylaniline and chloroacetone.<sup>8</sup> Oxidation of allylated oxindoles (*S*)-**5** (OsO<sub>4</sub>, NMO, then NaIO<sub>4</sub>) provided the aldehyde (*S*)-**24** in 92% yield. Two recrystallizations from isopropyl alcohol–cyclohexane furnished enantiopure (*S*)-**24** in 66% overall yield from oxindole **5**. Reductive cyclization of (*S*)-**24** using conditions optimized by Overman afforded (-)-esermethole, which has been transformed to (-)-physostigmine<sup>1b</sup> and (-)-pheneserine<sup>9</sup> in two steps. Thus, our work constitutes a formal total synthesis of (-)-physostigmine and (-)-pheneserine, a clinically more promising candidate, in seven total steps from commercially available starting materials.

In summary, we have developed the first enantioselective Mo-catalyzed AAA reaction for the generation of quaternary stereocenters at a prochiral nucleophile, in this case the 3-position of 3-alkyl oxindoles. The reaction is successful with a variety of alkyl substitutions, and its utility can be seen in the synthesis of (-)-physostigmine.

**Acknowledgment.** We thank the National Science Foundation and National Institute of Health (NIH-13598), for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California, San Francisco, supported by the NIH Division of Research Resources

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>

## References

- (1) (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
- (2) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363 and references therein.
- (3) (a) Trost, B. M.; Randinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (c) Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492. (d) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308.
- (4) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. For a review, see: Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159. Also see: Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141–144. Malkov, A. V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Tetrahedron Lett.* **2001**, *42*, 509.
- (5) Hughes, D. L.; Lloyd-Jones, G. C.; Kraska, S. W.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Mathre, D. J.; Reamer, R. A.; *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.
- (6) Jobst, J.; Hesse, O. *Ann. Chem. Pharm.* **1864**, *129*, 115.
- (7) We have previously observed that excess amount of base enhanced both ee and yield in the Pd-catalyzed AAA reaction of ketone enolate, presumably due to the formation of favorable lithium enolate mixed aggregates. Trost, B. M.; Schroeder, G. M. *Chem. Eur. J.* **2005**, *11*, 174.
- (8) Underwood, R.; Prasad, K.; Repic, O.; Hartmann, G. E. *Synth. Commun.* **1992**, *22*, 343.
- (9) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.

JA060560J