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An Asymmetric Hetero-Claisen Approach to 3-Alkyl-3-aryloxindoles

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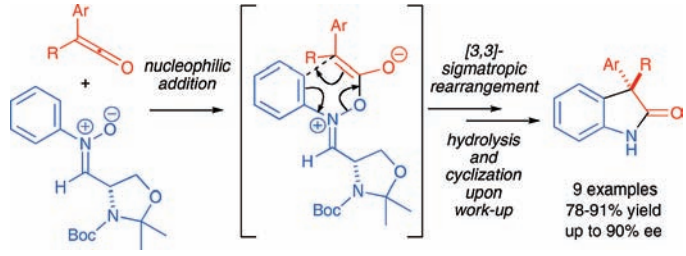
ABSTRACT



The reaction of a chiral *N*-phenylnitrone derived from Garner's aldehyde with alkylarylketenes generates 3-alkyl-3-aryloxindoles directly in excellent yields and with good to excellent levels of enantioselectivity (up to 90% ee).

3,3-Difunctionalized oxindoles are widely recognized as valuable synthetic intermediates, forming the core of numerous natural products and medicinal targets.[1] As a representative subclass, 3-alkyl-3-aryloxindoles are readily derivatized to the central motif of a range of hexahydropyrroloindole alkaloids that display an array of biological activities and present significant challenges for asymmetric total synthesis.[2] A number of strategies for the synthesis of the 3-alkyl-3-aryloxindole motif in both racemic and enantiomerically enriched form have been developed in recent years, including Pd-catalyzed asymmetric intramolecular Heck cyclization,[3] Pd-mediated asymmetric allylation,[4] Pd-catalyzed arylation[5] and alkylation,[6] direct C−H/Ar−H coupling methods,[7] and oxidative rearrangements,[8] among a host of others.[9]

The [3,3]-sigmatropic rearrangement of *O*-allyl indolyl ethers is an elegant alternative process to prepare 3-substituted oxindoles.[10] Classically, the Brunner oxindole synthe-

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(9) For select examples, see: (a) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4599. (b) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. (c) Munusamy, R.; Dhathathreyan, K. S.; Balasubramanian, K. K.; Venkatachalam, C. S. *J. Chem. Soc., Perkin Trans 2* **2001**, 1154. Fu and Vedejs have elegantly shown that heterocyclic compounds can promote catalytic asymmetric *O*- to *C*-carboxyl group transfer of indolyl carbonates: (d) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (e) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (f) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14.

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sis[11] generates 3-substituted oxindoles from acyclic reaction precursors, though elevated reaction temperatures are required to promote this transformation. A number of related 3-oxa-4-aza-[3,3] sigmatropic rearrangements have been developed that require the formation of a metal enolate or forcing reaction conditions to promote the rearrangement and generate racemic oxindoles.[12] An alternative hetero-Claisen-type process,[13] first investigated by Staudinger,[14] and subsequently by Lippman[15] and Taylor,[16] employs the reaction of phenylnitrone with 2 equiv of diphenylketene, generating 3,3-diphenyloxindole after methanolysis. Only limited use of this transformation has been made despite its potential synthetic versatility,[17] and to the best of our knowledge, no examples of this process using unsymmetrical disubstituted ketenes or asymmetric versions of this reaction have been demonstrated. Herein, we detail the development of an efficient, metal-free, asymmetric variant of this reaction that generates 3-alkyl-3-aryloxindoles with high enantiopurity (up to 90% ee) (Figure 1).

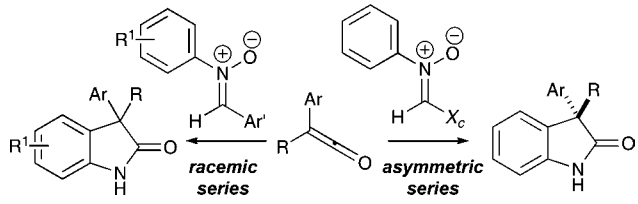

Figure 1. Proposed synthesis of 3-alkyl-3-aryloxindoles (X_c = stereodirecting group).

Initial studies focused upon the demonstration of this process in the racemic series. In an optimized procedure, treatment of nitrone **1** with methylphenylketene gave (±)-3-methyl-3-phenyloxindole **5** and 4-bromobenzaldehyde directly after workup, furnishing (±)-**5** in 85% isolated yield. This reaction proved general, tolerating a range of C(2)-aryl and C(2)-alkyl substituents within the ketene component, generating (±)-oxindoles **6**−**12** in excellent isolated yield (83−90%). A range of *N*-aryl nitrones are also tolerated, with 4- or 2-substituted *N*-aryl nitrones **2**−**4** giving the (±)-5- or (±)-7-substituted oxindoles **13**−**15**, respectively, in excellent yield (87−93%) (Figure 2).

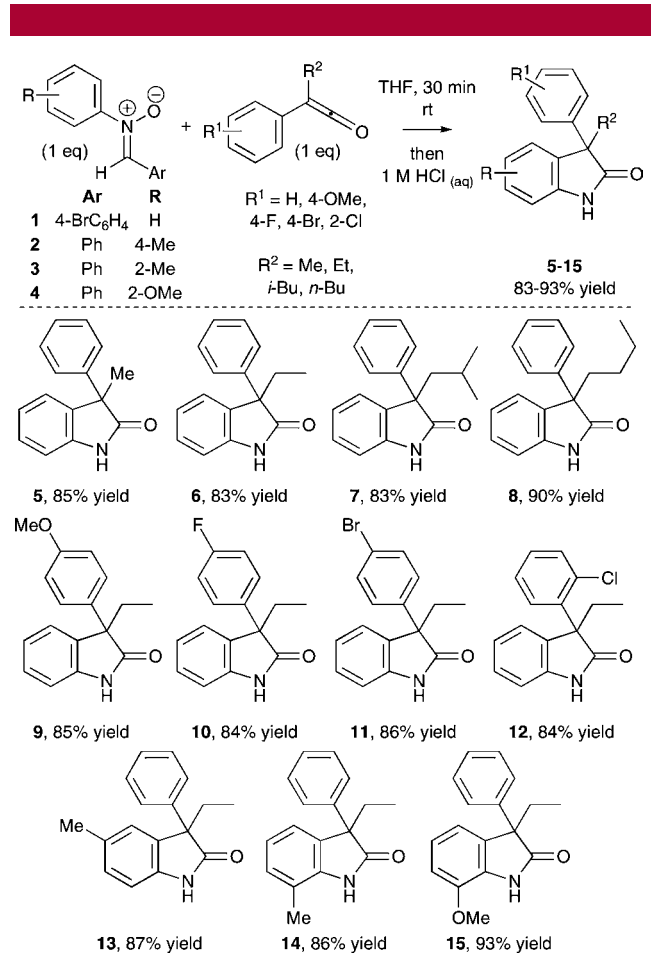

Figure 2. Synthesis of (±)-3-alkyl-3-aryloxindoles.

With an efficient synthetic protocol developed to generate (±)-3-alkyl-3-aryloxindoles, the ability of a chiral nitrone to induce asymmetry in this transformation was investigated. Treatment of Garner's aldehyde[18] with phenylhydroxylamine and $MgSO_4$ gave (*R*,*Z*)-*N*-phenylnitrone **16** as a bench stable crystalline solid as a single diastereoisomer in 87% yield. The (*Z*)-configuration within **16** was confirmed by single-crystal X-ray diffraction (Scheme 1).[19]

Treatment of nitrone **16** with methylphenylketene (1 equiv) followed by aqueous workup afforded oxindole (*S*)-**5** in 85% yield and 87% ee[20] and recovered Garner's aldehyde in 80%

(10) For representative examples, see: Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzuno, M.; Ogawa, A. *Chem. Commun.* **2006**, 420. Kawasaki, T.; Ogawa, A.; Terashima, R.; Saheki, T.; Ban, N.; Sekiguchi, H.; Sakaguchi, K-E. M. *J. Org. Chem.* **2005**, *70*, 2957. Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, H.; Sakamoto, M. *Tetrahedron Lett.* **1996**, *42*, 7525. For a recent catalytic asymmetric Meerwein−Eschenmoser Claisen rearrangement, see: Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162.

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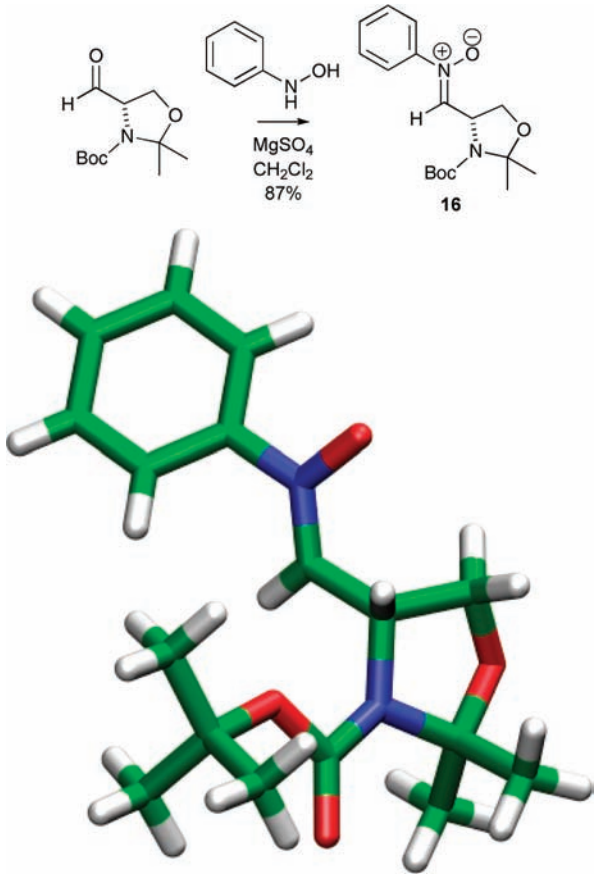
(16) Hafiz, M.; Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1700. Stokes, D. P.; Taylor, G. A. *J. Chem. Soc. C* **1971**, 2334. Pratt, R. N.; Stokes, D. P.; Taylor, G. A. *J. Chem. Soc. C.* **1968**, 1653.

(17) For examples of related reactions that generate achiral oxindoles, see: Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 3017. Baker, A. D.; Wong, D.; Lo, S.; Bloch, M.; Horozoglu, G.; Goldman, G. L.; Engel, R.; Liotta, D. C. *Tetrahedron Lett.* **1978**, *19*, 215. Calder, I. C.; Williams, P. J. *J. Chem Soc., Chem. Commun.* **1972**, 891.

(18) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.

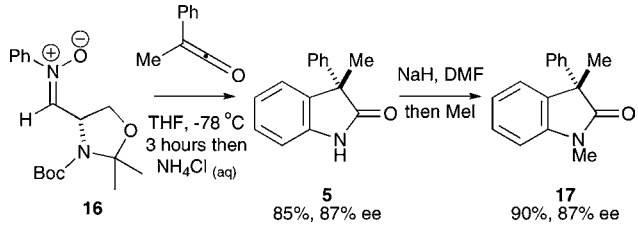
(19) Crystallographic data for compound **16** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 737167. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

Scheme 1. Preparation and Molecular Representation of the Single-Crystal X-Ray Structure of Nitrone **16**



yield. The absolute configuration within **5** was assigned by N-methylation to give the known *N*-methyloxindole **17** and comparison of its specific rotation with the literature[21] (Scheme 2).

Scheme 2. Asymmetric Oxindole Formation



The generality of this asymmetric process was next probed through treatment of nitrone **16** with a series of alkylarylketenes. A range of C(2)-aryl groups incorporating electron-donating and -withdrawing substituents, plus C(2)-alkyl substituents within the ketene component, are tolerated, generating the corresponding (*S*)-3-alkyl-3-aryloxindoles[22] in excellent isolated yield (78−91%) and 78−90% ee. Garner's aldehyde was recovered in 78−87% yield in each case (Figure 3).[23]

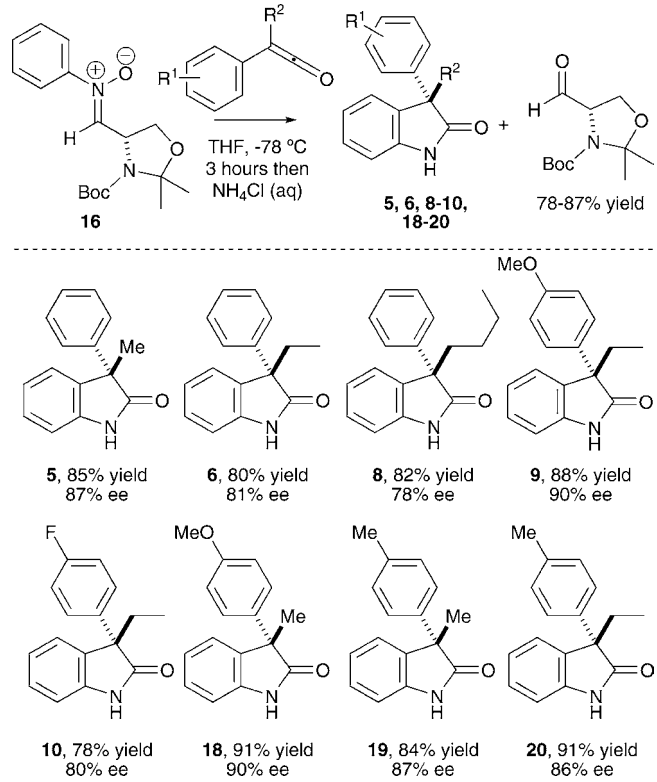


Figure 3. Asymmetric oxindole synthesis: generality.

A mechanistic proposal for this reaction is outlined in Figure 4. Nucleophilic addition of nitrone **16** to the ketene,

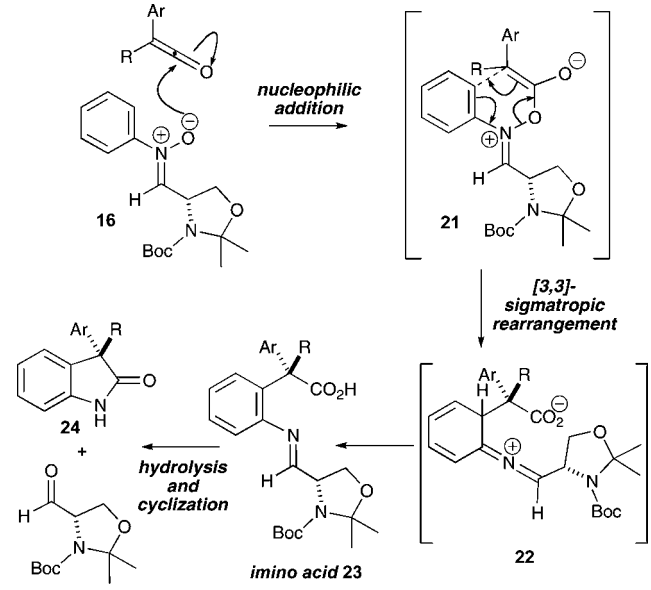


Figure 4. Mechanistic proposal for asymmetric oxindole synthesis.

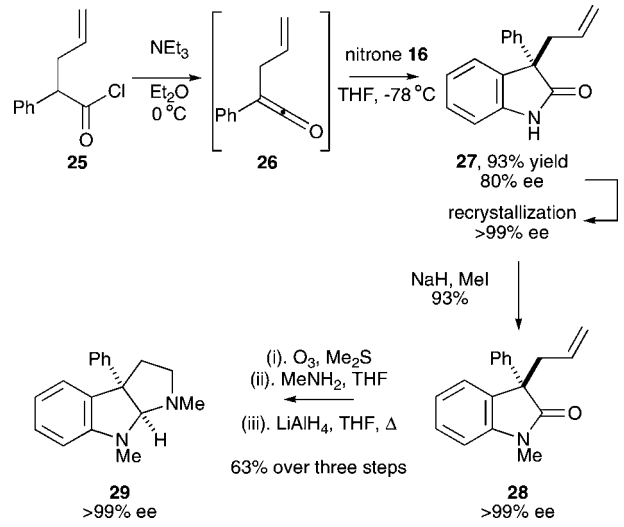
preferentially *anti*- to the C(2)-aryl substituent,[24] will generate the corresponding enolate **21**. Subsequent asymmetric [3,3]-sigmatropic rearrangement proceeds under the control

of the remote stereodirecting group to generate, after aromatization, the imino acid **23** that undergoes facile hydrolysis and cyclization upon workup to generate the enantioenriched 3-alkyl-3-aryloxindole **24** and Garner's aldehyde.[25]

To exemplify the experimental simplicity of this protocol, and its potential utility in synthesis, its application to the rapid construction of the 3-phenyl-hexahydropyrroloindole skeleton from simple starting materials was undertaken. Allylphenylketene **26** was prepared in situ by dehydrohalogenation of 2-phenylpent-4-enoyl chloride **25** and treated with nitrone **16** at −78 °C, generating (*S*)-3-allyl-3-phenyloxindole **27** in 93% yield and 80% ee,[26] with recrystallization giving (*S*)-**27** in >99% ee. N-Methylation gave **28** in 93% yield and >99% ee, with ozonolysis, in situ treatment with methylamine, and subsequent $LiAlH_4$ reduction giving **29** in 63% yield over three steps (Scheme 3).[27]

In conclusion, we have developed a simple synthetic procedure for the asymmetric synthesis of 3-alkyl-3-aryloxindoles (up to 90% ee). Further applications of this methodology in natural product synthesis, studies directed toward understanding how the remote stereocenter controls the facial selectivity of this transformation, and the development of catalytic asymmetric variants are currently underway within this laboratory.

Scheme 3. Synthetic Utility of Asymmetric Oxindole Synthesis



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Supporting Information Available: Experimental procedures plus spectroscopic and HPLC data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) As shown by HPLC analysis with reference to an authentic racemic sample, see Supporting Information for full details.

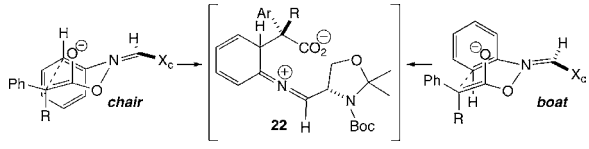
(21) $[\alpha]_D^{20}$ −81.2 (c = 1.1, CH_2Cl_2), 87% ee; lit.[5e] $[\alpha]_D^{23}$ −86.0 (c = 1.00, CH_2Cl_2), 94% ee; see Supporting Information for full details.

(22) The absolute configurations within **6**, **8**−**10**, and **18**−**20** were assigned by analogy to that proven for **5**. All ee values were measured by HPLC analysis with reference to authentic racemic samples; see Supporting Information for full details.

(23) The specific rotation of recovered Garner's aldehyde {$[\alpha]_D^{20}$ −75.4 (c = 1.00, $CHCl_3$)} was equivalent {$[\alpha]_D^{20}$ −76.3 (c = 0.89, $CHCl_3$)} to that used to prepare nitrone **16**, consistent with no racemization of the stereodirecting fragment during the rearrangement.

(24) For theoretical studies concerning the selectivity of nucleophilic additions to ketenes, see: Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 10992.

(25) Assuming a concerted [3,3]-sigmatropic rearrangement, we cannot currently distinguish between potential chair- and boat-type transition states that would both lead to the correct absolute configuration of the oxindole product and would have the opposite configuration at the stereocenter within **22** that is lost upon rearomatization. Using this framework, it is also not clear how the remote stereocenter influences the facial selectivity of this reaction; this is the focus of current investigations.



(26) The absolute (*S*)-configuration of **27** was assigned both by analogy to that proven for **5** and unambiguously through its conversion to (*S*)-1-benzyl-3-(2-hydroxyethyl)-3-phenylindolin-2-one via N-benzylation, ozonolysis, and $NaBH_4$ reduction and comparison of the HPLC retention times with that of the literature (see Overman et al.; ref 3); see Supporting Information for full details.

(27) The enantiopurity of **29** could not be assigned unambiguously by HPLC analysis but was assigned as >99% ee on the assumption that no racemization had taken place in the conversion from **28**. The absolute configuration within **29** was assigned by comparison of its specific rotation with the literature (see Maruoka et al., ref 9a); $[\alpha]_D^{20}$ +114.2 (c = 1.06, $CHCl_3$); lit.[9a] $[\alpha]_D^{23}$ +111.63 (c = 0.62, $CHCl_3$), 90% ee; see Supporting Information for full details.