J|A|C|S
COMMUNICATIONS

Published on Web 11/07/2007

Mo-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation of 3-Aryloxindoles

Barry M. Trost* and Yong Zhang

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

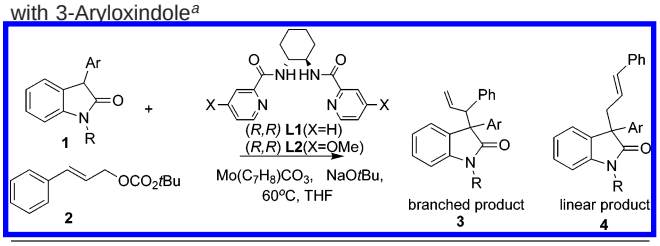
Received August 3, 2007; E-mail: bmtrost@stanford.edu

The asymmetric formation of a quaternary carbon represents one of the most difficult challenges in asymmetric catalysis.[1] Perhaps the most successful strategy is the use of asymmetric copper catalysts; especially with respect to conjugate additions involving nonstabilized nucleophiles.[2] This problem is further aggravated when an adjacent tertiary center must be formed asymmetrically concurrently. Creating such molecular complexity in a single step is a daunting challenge. Our recent success in accomplishing this in Pd-catalyzed allylation of enolates[3] with meso-like 1,3-disubstituted allyl electrophiles encouraged us to question whether monosubstituted allyl electrophiles may be employed to give products of attack at the more substituted allyl terminus to give the branched product. For a process of this kind, molybdenum catalysis[4] appears more appropriate; however, the large steric demand of a fully substituted enolate would clearly stress this regioselectivity issue. In this communication, we describe the alkylation of the anions of 3-aryloxindoles with monosubstituted allyl carbonates in the presence of a chiral molybdenum catalyst. The products of this reaction, containing highly functionalized chiral oxindoles, should provide new avenues toward asymmetric preparations of biologically important indole alkaloids.[5]

Initial optimization was focused on the *N*-Boc-3-phenyloxindole (**1a**) as the nucleophile. However, a modest regio- and diastereoselectivity were obtained (Table 1, entry 1). The use of slightly less stabilized *N*-alkyloxindoles (entries 2−4) improved the selectivity, especially the regioselectivity of the reaction, dramatically. The steric size of the N-protecting group does not seem to be important as methoxymethyl (entry 2), benzyl (entry 3), and methyl (entry 4) gave essentially identical results. An interesting trend emerged, however, when we systematically modified the electronics of the 3-aryl substituents on the oxindoles (entries 4−9). The regio- and diastereoselectivity of the reaction significantly decreased as more electron-withdrawing *para*-substituents were placed on the phenyl ring (entries 5−7). Electron-donating groups (entries 8 and 9), however, had little effect on the selectivity.[6] In all cases, the ee and yield of the reaction showed little sensitivity to the electronic variations.

To determine the steric effects of the nucleophiles, we examined the reactions with several sterically distinct oxindoles (Table 1, entries 10−20). At the outset, we expected that, for steric reasons, smaller nucleophiles would be more selective toward bond formation at the more hindered internal position of the π-allyl, compared to more bulky ones. In contrast to this expectation, the bulky 2-tolyl and 1-naphthyl substituted oxindoles gave excellent selectivity (entries 10 and 11), while the smaller thienyl, indolyl, and thiazoyl substituted ones gave exclusively linear products (entries 13−15). Interestingly, installing extra steric bulk on these heterocycles reversed the regioselectivity to give branched products with excellent diastereo- and enantioselectivity (entries 16−19). Curiously, a *N*-tosyl substituted 3-indolyloxindole also gave very high b/l selectivity (entry 20). It is worth noting that bulkier oxindoles also gave better diastereoselectivity (entry 10 vs 4, entry 11 vs 12).

Table 1. Steric and Electronic Effects for the Mo-AAA Reaction with 3-Aryloxindole[a]



entry	Ar	R	b/l	dr	ee[b]	yield[c]
1	Ph (**1a**)	Boc	5:1	5:1	93%	91%
2	Ph (**1b**)	MOM	19:1	7:1	92%	90%
3	Ph (**1c**)	Bn	17:1	9:1	90%	85%
4	Ph (**1d**)	Me	18:1	8:1	92%	88%
5	4-F−Ph (**1e**)	Me	16:1	6:1	91%	90%
6	4-Cl−Ph (**1f**)	Me	13:1	5.5:1	95%	88%
7	4-CN−Ph (**1g**)	Me	7:1	4.5:1	89%	84%
8	4-MeO−Ph (**1h**)	Me	18:1	8:1	92%	92%
9	4-NMe_2-Ph (**1i**)	Me	17:1	6:1	92%	87%
10	2-Me−Ph (**1j**)	Me	17:1	19:1	94%	90%
11	1-naphthyl (**1k**)	Me	15:1	19:1	95%	88%
12	2-naphthyl (**1l**)	Me	15:1	6:1	90%	90%
13	2-thiophyl (**1m**)	Me	0:1	−	0%	90%
14	*N*-Me-3-indolyl (**1n**)	Me	0:1	−	−	82%
15	2-Ph-5-thiazoyl (**1o**)	Bn	0:1	−	−	86%
16	3-Me-2-thiophyl (**1p**)	Me	11:1	19:1	92%	95%
17	*N*-Me, 2-Ph-3-indolyl (**1q**)	Me	9:1	19:1	94%	65%
18	2,4-dimethyl-5-thiazoyl (**1r**)	Me	2.5:1	19:1	92%	84%
19	2,4-diphenyl-5-oxazoyl (**1s**)	Me	16:1	19:1	96%	83%
20	*N*-tosyl-3-indolyl (**1t**)[7]	Me	10:1	19:1	97%	63%
21[d]	**1r**	Me	16:1	19:1	93%	86%
22[d]	**1g**	Me	18:1	4:1	92%	85%

[a] Reaction performed with $Mo(C_7H_8)(CO)_3$ (10 mol %), ligand **L1** (15 mol %), and oxindoles/cinnamyl *tert*-butyl carbonate/base (1/1.1/1:1) at 60 °C in THF. [b] Determined by chiral HPLC. [c] Isolated yields of allylated oxindoles. [d] Reaction performed with ligand **L2**.

The trends observed in the above electronic and steric studies are rationalized by a reaction mechanism involving divergent reaction modes of O-bound and C-bound molybdenum enolate complexes (Figure 1), both of which have been structurally characterized.[8−10] Electronic and steric variations of the nucleophile may influence the equilibrium ratios of the two enolate isomers and which isomer reacts to give the product.[11] Sterically, a larger aryl group should disfavor the crowded C-bound enolate and favor the O-bound enolate structure. In this case, the lower steric strain allows the more substituted allyl terminus to bond to the sp^2 carbon of the enolate to form the normally preferred branched product via a favorable "Claisen-like" transition state.[12] On the other hand, the more compact five-membered heterocycle substituted oxindoles should accommodate the C-bound enolate more readily. The steric crowding of a reductive elimination to a quaternary sp^3 center only allows bonding to the less hindered primary allyl terminus in this

10.1021/ja0755717 CCC: $37.00

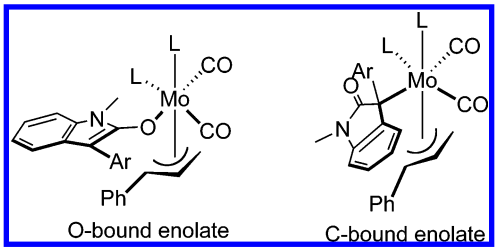


Figure 1. Mo enolate structures.

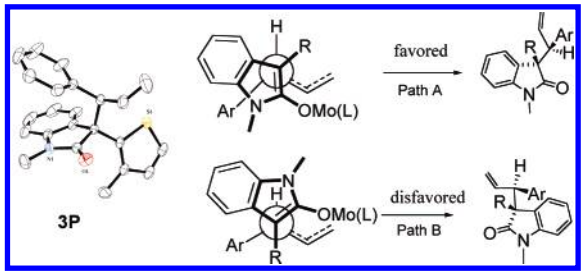
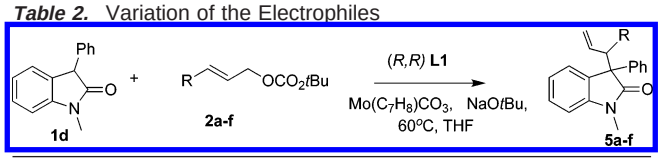


Figure 2.

Table 2. Variation of the Electrophiles



entry	R	b/l	dr	ee	yield
1	3,4$Cl_2C_6H_3$ (**a**)	6:1	5.5:1	89%	87%
2	4-OTBSC_6H_4 (**b**)	19:1	8:1	89%	90%
3	2-furyl (**c**)	12:1	6:1	91%	92%
4	2-thiophyl (**d**)	13:1	8:1	90%	88%
5	2-NHBocC_6H_4 (**e**)	19:1	19:1	93%	89%
6	2-(*E*)-butene (**f**)	6:1	6:1	91%	84%

case. Electronically, electron-withdrawing 3-aryl substituents should stabilize both enolate complexes and slow down their interconversion.[13,14] Hence, we see a partial linear relationship between the electronic property of the *para*-substituent and the regioselectivity of the reaction.[6] Furthermore, a more electron-rich molybdenum should disfavor the reductive elimination and promote the equilibration between the two isomers. On the basis of this hypothesis, the electron-rich bismethoxypyridine ligand should move toward a Curtin−Hammett-type situation and favor reductive elimination via the less hindered O-bound enolate to give the branched product as observed (entry 22 vs 7, entry 21 vs 18).[15]

Several other aromatic, heteroaromatic, and polyenyl carbonates also functioned well with oxindole **1d** (Table 2). The reaction is tolerant of a number of functional groups on the electrophile, and good to excellent selectivity is observed for all substrates.

The relative and absolute stereochemistry was established by X-ray crystallographic analysis of the product of entry 16 as shown in Figure 2. Between the two depicted paths, path A is clearly favored as the least sterically demanding in the transition state. This stereochemical outcome is also consistent with our previous reports.[4]

In conclusion, we have reported a molybdenum-catalyzed allylic alkylation reaction with oxindoles that proceeds with high regio-, diastereo-, and enantioselectivity. The products of this reaction, containing a quaternary center at the 3 position of the oxindole as well as a vicinal tertiary center that are difficult to access via other methods, are well suited for further elaborations toward indole alkaloids. The correlation between the electronics and sterics of the nucleophile and the regio- and diastereoselectivity of the reaction is highly unusual and provides the exciting prospect that, by careful tuning of the nucleophile, great regio- and diastereocontrol of the reaction can be exercised. The preference for bond formation at the more substituted position of the π-allyl with even extremely bulky nucleophiles is also noteworthy.

Acknowledgment. We thank the National Science Foundation and National Institutes of Health (NIH-13598) for their generous support of our programs. Y.Z. thanks Amgen for a graduate fellowship. 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) For recent reviews of catalytic asymmetric methods that generate quaternary centers, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.

(2) For a few recent examples, see: (a) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097. (b) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. (c) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774.

(3) For asymmetric allylic alkylations with Pd, see: (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. For Ir, see: (b) Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720. For W, see: (c) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. For Cu, see: (d) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676.

(4) (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (c) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944. (d) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.

(5) (a) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 14, pp 163−236. For previous examples of catalytic asymmetric methods that generate quaternary centers at the 3 position of oxindoles, see: (b) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (c) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008. (d) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, 44, 308.

(6) See Supporting Information for a Hammett plot of the regioselectivity with electronically differentiated oxindoles.

(7) The enolate of **1t** is not stable above rt. The reaction was performed at rt with 20% catalyst loading.

(8) For mechanistic studies of the Mo reaction, see: (a) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 702. (b) Hughes, D. L.; Lloyd-Jones, G. C.; Krska, 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.

(9) For recent X-ray characterizations of molybdenum enolate complexes, see: (a) O-bound enolate: Morales, D.; Clemente, M. E. N.; Perez, J.; Riera, L.; Riera, V. *Organometallics* **2003**, *22*, 4124. (b) C-bound enolate: Cameron, P. A.; Britovsek, G. J. P.; Gibson, V. C.; Williams, D. J.; White, A. J. P. *Chem. Commun.* **1998**, 737, and references cited therein.

(10) For examples of divergent reactivity of transition metal enolate complexes, see: (a) Campora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Gutierrez-Puebla, E.; Ruiz, C. *J. Am. Chem. Soc.* **2003**, *125*, 1482. (b) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3344.

(11) For a discussion of electronic and steric effects on reductive elimination from Pd complexes, see: Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

(12) Such mechanism has been proposed in the π-allyl reactions with mercurial acetate: Kitching, W.; Sakakiyama, T.; Rappoport, Z.; Sleezer, P. D.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1972**, *94*, 2239.

(13) The interconversion of C-enolate and O-enolate has been postulated to occur through an η-3 oxoallyl complex: Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5670.

(14) Kinetic measurements of the equilibration between C-enolate and O-enolate have been carried out for Ru-enolate complex[13] and Ni-enolate complex[10a].

(15) For a study of the electronic effects of the pyridine ring in the ligand, see: Belda, O.; Moberg, C. *Synthesis* **2002**, 1601.

JA0755717