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

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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 non-stabilized 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 towards 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 diastereo-selectivity were obtained (Table 1, entry **1**). The use of slightly less stabilized N-alkyl oxindoles (entry **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 (entry **4-9**). The regio-and diastereo-selectivity of the reaction significantly decreased as more electron-withdrawing para-substituents were placed on the phenyl ring (entry **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 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, entry **10-20**). At the outset, we expected that for steric reasons, smaller nucleophiles would be more selective towards 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-naphthy 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 (entry **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 diastereoselecitivity (entry 10 vs. 4, entry 11 vs. 12).

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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-member 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 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. Based on this hypothesis, the electron-rich bis-methoxypyridine ligand should move towards 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 towards indole alkaloids. The correlation between the electronics and sterics of the nucleophile and the regio- and diastereo-selectivity of the reaction is highly unusual and provides the exciting prospect that by careful tuning of the nucleophile, great regio- and diastereo-control 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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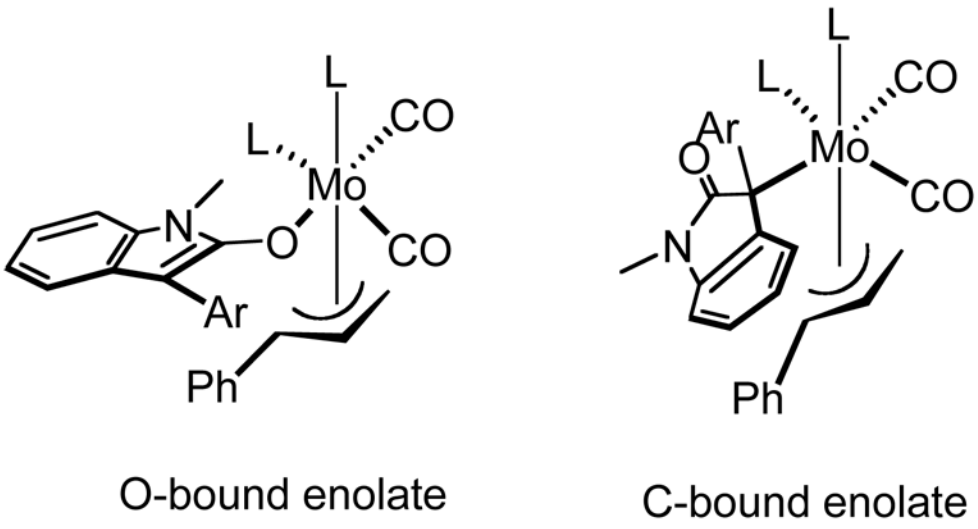



**Figure 1.**
Mo enolate structures

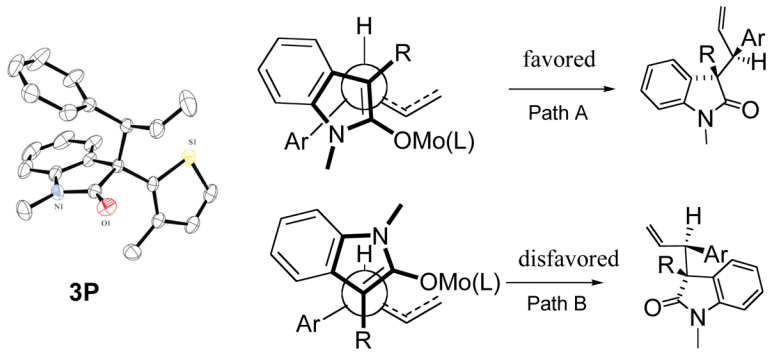
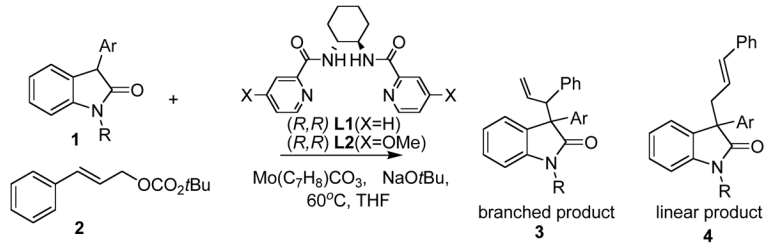



**Figure 2.**

**Table 1**

Steric and Electronic effects for the Mo-AAA reaction with 3-aryloxindole[a]




| entry | Ar | R | b/l | d.r. | 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-Napth**(1k)** | Me | 15:1 | 19:1 | 95% | 88% |
| 12 | 2-Napth **(1l)** | Me | 15:1 | 6:1 | 90% | 90% |
| 13 | 2-thioph **(1m)** | Me | 0:1 | ---- | 0% | 90% |
| 14 | *N*-Me-3-indoly**(1n)** | Me | 0:1 | ---- | ---- | 82% |
| 15 | 2-Ph-5-thiazoyl **(1o)** | Bn | 0:1 | ---- | ---- | 86% |
| 16 | 3-Me-2-thioph**(1p)** | Me | 11:1 | 19:1 | 92% | 95% |
| 17 | *N*-Me, 2-Ph-3-indoly**(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-indoly(**1t**)[7] | Me | 10:1 | 19:1 | 97% | 63% |
| 21[e] | **1r** | Me | 16:1 | 19:1 | 93% | 86% |
| 22[e] | **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.

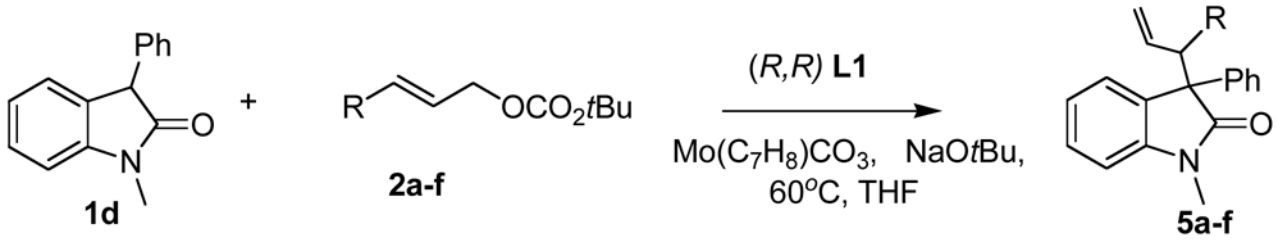
[b] Determined by chiral HPLC.

[c] Isolated yields of allylated oxindoles.

[e] Reaction performed with ligand **L2**.

**Table 2**

Variation of the electrophiles




| entry | R | b/l | d.r. | ee% | yield% |
|---|---|---|---|---|---|
| 1 | 3,4$Cl_2C_6H_3$**(a)** | 6:1 | 5.5:1 | 89% | 87% |
| 2 | 4-OTBS$C_6H_4$**(b)** | 19:1 | 8:1 | 89% | 90% |
| 3 | 2-furyl**(c)** | 12:1 | 6:1 | 91% | 92% |
| 4 | 2-thioph**(d)** | 13:1 | 8:1 | 90% | 88% |
| 5 | 2-NHBoc$C_6H_4$**(e)** | 19:1 | 19:1 | 93% | 89% |
| 6 | 2-(*E*)butene**(f)** | 6:1 | 6:1 | 91% | 84% |