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Published on Web 02/20/2007

Design and Synthesis of Modular Oxazoline Ligands for the Enantioselective Chromium-Catalyzed Addition of Allyl Bromide to Ketones

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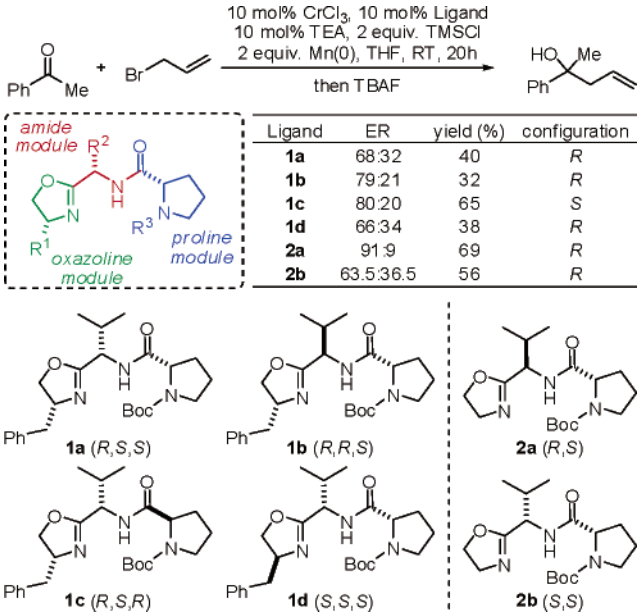
The catalytic asymmetric addition of allyl fragments to carbonyl substrates has proven to be a powerful method for the synthesis of enantiomerically enriched homoallylic alcohols.[1] While many successful variants of this transformation have been reported for aldehyde allylation,[2] only recently has carbonyl allylation been extended to ketones. This is presumably due to the inherent difficulty in differentiation of the enantiotopic faces of a ketone as compared to those of an aldehyde. In recently reported examples, a range of nucleophilic allyl sources can be used including boranes,[3] stannanes,[4] and silanes.[5] However, there are no catalytic examples using allylic halides,[6] which are generally the synthetic precursors to these nucleophilic allyl sources. Herein we report the discovery of a chromium-catalyzed enantioselective ketone allylation reaction where allylic bromides are used directly.

On the basis of our success using oxazoline ligands of type **1** in the chromium-catalyzed enantioselective addition of allylic halides to aldehydes (Nozaki−Hiyama−Kishi reaction),[7] we chose to explore this ligand template for enantioselective ketone allylation reactions (Figure 1).[8] These ligands contain an oxazoline, amide, and proline module and can be readily synthesized using α-amino acid derivatives allowing for rapid and systematic optimization of the ligand structure.[9] The optimal ligand for aldehyde allylation **1a** was initially probed for ketone allylation using acetophenone as the model substrate. Excitingly, a 68:32 enantiomeric ratio (ER) of the tertiary alcohol product was observed (Figure 1, ligand **1a**) without modification to the original aldehyde allylation conditions.[8]

On the basis of our previous studies, we anticipated that the most significant changes in enantiomeric ratio as a function of ligand structure would be observed when altering ligand relative stereochemistry. Therefore, all four diastereomers of ligand **1** were synthesized and evaluated for acetophenone allylation. The relative configuration of the chiral centers on the ligand has a significant effect on the enantiomeric ratio and absolute configuration of the product. Specifically, the configuration of the proline module directly influences the facial selectivity of the reaction. For example, comparing the use of ligand **1a** versus **1c**, where the proline configuration is inverted, results in the opposite facial selection. A similar effect is observed comparing ligands **1b** and **1d**, although in this case, the configuration of proline remains constant and the other two centers are inverted. In contrast, the chiral center on the oxazoline ring only subtly impacts the enantioselective outcome. For example, inverting the chiral center on the oxazoline module in **1a** as compared to **1d** results in only a 4% ee difference. This observation is intriguing considering the oxazoline substituent dramatically effects both the absolute configuration and enantiomeric ratio of the product in aldehyde allylation.[8]

Considering the present results from acetophenone allylation, it was hypothesized that the oxazoline substituent is not an important structural feature for affecting asymmetric induction. Therefore, a truncated ligand, with the chiral center on the oxazoline module removed, was synthesized in a three-step process starting with valine



Ligand	ER	yield (%)	configuration
1a	68:32	40	*R*
1b	79:21	32	*R*
1c	80:20	65	*S*
1d	66:34	38	*R*
2a	91:9	69	*R*
2b	63.5:36.5	56	*R*

Figure 1. Evaluation of ligand diastereomers and truncation of the ligand structure in the enantioselective allylation of acetophenone.

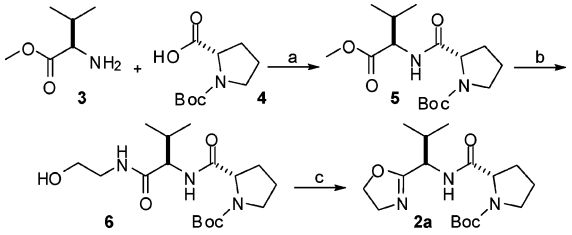
derivative **3** and proline derivative **4** (Scheme 1). After peptide coupling[10] and nucleophilic addition of glycinol to the resulting ester **5**, oxazoline formation was accomplished under Mitsunobu-type conditions.[11] This synthetic sequence is significantly more efficient than our previous method for synthesizing ligand **1a**.[8]

To our delight, evaluation of the truncated ligand **2a** revealed an increase in the enantiomeric ratio of the acetophenone allylation product (ER = 91:9). The diastereomer of ligand **2a**, ligand **2b**, was then synthesized and evaluated to obtain information on the relative stereochemistry of the two chiral centers in the truncated ligand framework. Again, the relative stereochemistry of the proline and the amide modules had a considerable effect on the ER (**2a**, 91:9 vs **2b**, 63.5:36:5).

Optimization of the catalyst system using ligand **2a** and acetophenone led to the use of 4 equiv of TMSCl,[12] which increases the isolated yield with no detrimental effects on ER. Lowering the reaction temperature from room temperature to 0 °C enhanced the ER to 96:4 (Table 1, entry 1). Using these optimal conditions, the scope was evaluated. We found that aryl ketones are excellent substrates for the transformation, as is highlighted by a 95% yield and a 96:4 ER for the allylation of 2-acetonaphthone (entry 6). The nature and placement of the substituent on the aryl ring has little effect on the enantioselective outcome of the reaction (entries 2−6) though α-tetralone is a poor substrate using this system (entry 7). Additionally, halide-containing compounds are tolerated, providing an additional synthetic handle for further functionalization and showcasing the chemoselective nature of the Nozaki−Hiyama−Kishi reaction (entries 2, 9, and 10). As can be seen in entries 8−10,

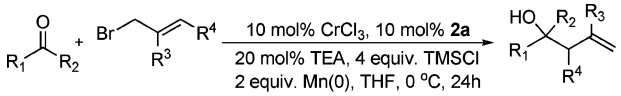
10.1021/ja068915m CCC: $37.00

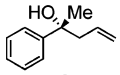
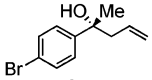
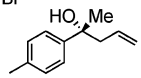
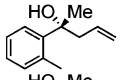
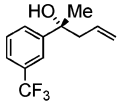
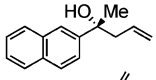
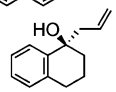
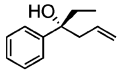
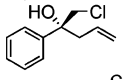
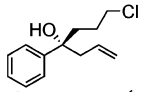
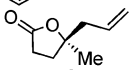
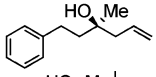
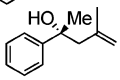
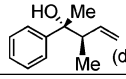
Scheme 1. Synthesis of Truncated Ligand **2a**[a]



[a] Reagents and conditions: (a) isobutyl chloroformate, NMM, CH_2Cl_2 (95%); (b) glycinol, $PhCH_3$/THF, reflux (95%); (c) PPh_3, DIAD, CH_2Cl_2 (85%).

Table 1. Substrate Scope



entry	product	yield (%)[a]	ee (%)[b]	ER[b]
1		82	92	96:4
2		73	90	95:5
3		94	86	93:7
4		83	87	93.5:6.5
5		63	91	95.5:4.5
6		95	92	96:4
7		64	59	79.5:20.5
8		77	93	96.5:3.5
9		56	90	95:5
10		66	91	95.5:4.5
11[c]		75	16	58:42
12		93	33	66.5:33.5
13		73	91	95.5:4.5
14	 (dr 3.8:1)	69	88 (*anti*) 70 (*syn*)	94:6 85:15

[a] Average of at least two experiments. [b] Determined either by GC or HPLC equipped with a chiral stationary phase. [c] Ethyl levulinate was used as the ketone substrate.

changing the nature of the non-aryl substituent does not erode the observed enantioselectivity and the highest ER is observed in entry 8. In contrast, poor enantiomeric ratios are observed for aliphatic ketones (entries 11 and 12) though it is important to highlight that the facial selection in these cases is reversed.[12] Other allylic halides, methylallyl and crotylbromide, were successfully added to acetophenone in similar enantiomeric ratios to that of allyl bromide (entries 13 and 14). A modest diastereoselection is observed for the addition of crotylbromide favoring the *anti* isomer (3.8:1).

In summary, by using a modular catalyst design, key structural features responsible for improving asymmetric induction were systematically tested. Evaluating ligand relative stereochemistry revealed that the oxazoline module had little effect on asymmetric catalysis. Therefore, a truncated ligand was synthesized and found to be highly effective for the first example of a chromium-catalyzed enantioselective addition of allylic bromides to aryl ketones. Currently, we are applying this approach to further explore and understand the influence of systematic structural changes on enantioselective outcomes and applying this knowledge to improving the scope of enantioselective ketone allylation as well as investigating other synthetically useful transformations.

Acknowledgment. This work was supported by the National Science Foundation through a CAREER award to M.S.S. (CHE-0132905). M.S.S. thanks the Dreyfus Foundation (Teacher-Scholar) and Pfizer for their support.

Supporting Information Available: Ligand synthesis, catalytic procedures, and enantiomeric excess determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA068915M