Diastereo- and Enantioselective Iridium-Catalyzed Allylation of Cyclic Ketone Enolates: Synergetic Effect of Ligands and Barium Enolates

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The reaction between methyl cinnamyl carbonate (4a) and 2-methyl-1-tetralone (5a) was investigated to evaluate the effects of the base and the ligand on reactivity and diastereoselectivity (Table 1). In the presence of [Ir(cod)Cl]$_2$, phosphoramidite 1a and silver phosphate 2, which led to diastereoselective reactions of azlactones, no reaction occurred between 4a and 5a in 1,2-dimethoxyethane (DME); presumably, the phosphate is not a sufficiently strong base to deprotonate the weak acidic tetralone (entry 1). In contrast, the same reaction run with stoichiometric amounts of lithium bis(trimethylsilyl)amide (LHMDS) as the base occurred smoothly to deliver the branched product exclusively in good yield. However, this reaction occurred with low dr (74%, 2.0:1, entry 2). When the reaction was conducted with the catalyst derived from ligand 1b, the diastereoselectivity was equally low (dr 2.3:1, entry 3). Considering that the different aggregation states of the enolates could potentially affect the diastereoselectivity of the reactions, we investigated reactions with other classes of metal enolates. 

Because of the positive effect of magnesium enolates on the diastereoselectivity in the allylation of thiazolones, we studied systematically the effect of the alkaline earth metal on the
Table 1. Effects of Ligand and Metal Enolates on the Ir-Catalyzed Allylation of 2-Methyl-1-tetralone

| entry | ligand | base | yield (%) | dr | ee (%) |
|-------|--------|------|-----------|----|--------|
| 1     | 1a     | none | 0         | 2:0:1 | |
| 2     | 1a     | LHMDS| 74        | 2.0:1 | |
| 3     | 1b     | LHMDS| 70        | 2:3:1 | |
| 4     | 1a     | Mg(Ot-Bu)₂ | 10       | 1:1:1 | |
| 5     | 1a     | Ca(Ot-Pr)₂ | 17       | 1:3:1 | |
| 6     | 1a     | Sr(Ot-Pr)₂ | 64       | 1:7:1 | |
| 7     | 1a     | Ba(Ot-Bu)₂ | 75       | 2:0:1 | |
| 8     | 1b     | Mg(Ot-Bu)₂ | 15       | 1:6:1 | |
| 9     | 1b     | Ca(Ot-Pr)₂ | 20       | 3:3:1 | |
| 10    | 1b     | Sr(Ot-Pr)₂ | 61       | 4:5:1 | |
| 11    | 1b     | Ba(Ot-Bu)₂ | 72       | 5:0:1 | 98 |
| 12  | 1b     | Ba(Ot-Bu)₂ | 83       | 9:0:1 | 98 |
| 13  | 1b     | Ba(Ot-Bu)₂ | 82 (81)  | 11:0:1 | 98 |
| 14  | 1b     | Ba(Ot-Bu)₂ | 83 (81)  | 11:0:1 | 98 |
| 15  | 1b     | Ba(Ot-Bu)₂ | 81       | 3:2:1 | 98 |

*1.00 equiv of cinnamyl carbonate, 1.20 equiv of 2-methyl-1-tetralone. See the SI for experimental details. Absolute configuration of the allylation product was determined by analogy. Determined by 1H NMR analysis of crude reaction mixtures. Determined by chiral HPLC analysis of the major diastereomer. THF instead of DME. *Reaction conducted at 5 °C. 2 mol% preformed catalyst 3 was used instead of the in situ-generated catalyst. *2.00 equiv of TMEDA was added under the same conditions as entry 14.

The effects of the two ligands on the diastereoselectivity, however, was distinct for reactions conducted with the Sr and Ba alkoxides. When barium enolates were employed as nucleophiles, the reaction conducted with the catalyst generated from ligand 1b occurred with higher diastereoselectivity (entry 11, dr 5:0:1) than that conducted with the catalyst generated from ligand 1a (entry 7, dr 2:0:1). Further investigation of the reaction conditions showed that the reaction conducted at 5 °C in THF yielded product 6a in 82% yield, 11:1 dr, and 98% ee (entry 13).

To identify the effect of the silver phosphate, we prepared the iridium cinnamyl complex 3 with preformed catalyst 3, the reaction furnished product 6a in yield, diastereoselectivity, and enantioselectivity (entry 14) that were comparable to those obtained with the catalyst formed in situ by the silver phosphate (entry 13). This result confirmed that the combination of ligand 1b and barium enolates is crucial to the level of stereoselectivity in this reaction and that the catalytic amount of silver salt 2 only promotes the formation of the active metallacyclic catalyst, rather than affecting stereoselectivity. Because the preformed Ir-cinnamyl complex is stable in air and easy to handle, the reaction scope was evaluated with the isolated complex 3 as the catalyst.

The effect of TMEDA was also investigated to probe the importance of aggregation state of metal enolates. In the presence of 2.0 equiv of TMEDA, the reaction occurred with much lower diastereoselectivity than the allylation of the barium ketone enolate in the absence of this additive (entry 15, 3.2:1 dr). Although merely suggestive at this point, this result is consistent with our hypothesis that the aggregation state of the enolates plays an important role in the control of diastereoselectivity.

Table 2 summarizes the scope of the nucleophile in the allylation with Ba enolates and catalyst 3 under the same conditions as entry 14.

Table 2. Ir-Catalyzed Allylation of Ketones

```
| R   | δ (%) | dr   | ee (%) |
|-----|-------|------|--------|
| 2 Ph | 95%   | >99% ee |
| 2 Me | 96%   | >99% ee |
| 2 MeO | 95% | >99% ee |
| 2 MeOH | 98% | >99% ee |
| 2 Bn | 95%, δ >20:1 | >99% ee |
| 2 Bn | 95% | >99% ee |
| 2 Bn | 81%, δ >5:1 | >99% ee |

Both the enolates and the allylcarbonates were cooled to 5 °C prior to mixing. See the SI for experimental details. Absolute configurations were assigned by analogy; dr’s were determined by 1H NMR analysis of the crude reaction mixtures; ee’s determined by chiral HPLC analysis. tert-Butyl cinnamylcarbonate as the substrate.
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yield with 12:1 dr and >99% ee (entry 8). The allylation reactions of aryl-substituted cyclohexanones occurred smoothly to give products in good yields, good diastereoselectivities, and excellent enantioselectivities (81%−85% yield, 5.5:1−9:1 dr, >99% ee, entries 9 and 10).

Table 3 summarizes the results of the reactions between 2-benzyl-1-tetralones and allylic carbonates under the standard conditions. The reactions of 4-substituted cinnamyl carbonates possessing diverse electronic properties showed little effect on stereoselectivity. For example, the substrate containing an electron-donating methoxy group furnished the product in 81% yield, 17:1 dr, and 99% ee (entry 1); cinnamyl carbonates containing electron-withdrawing groups, such as a trifluoromethyl, bromo, or fluoro substituent, afforded products in good yields and similar stereoselectivities (87%−95% yield, 11:1−15:1 dr, >99% ee, entries 2−4). 3-(2-Naphthyl)allyl carbonate and 3,4-dichlorocinnamyl carbonate also reacted similarly to other cinnamyl carbonates (82−93%, 10:1−12:1 dr, 98−99% ee, entries 5 and 6).

The reactions of electrophiles containing heteroaryl and alkenyl substituents were also examined. Allyl carbonates containing an electron-rich furyl group underwent the substitution reaction to give the product in 79% yield, 6:1 dr, 98% ee (entry 7). The allyl carbonate containing an electron-deficient and potentially coordinating pyridyl group also reacted to give the allylated product (90%, 6:1 dr, >99% ee, entry 8). Reactions with alkenyl-containing allyl carbonates furnished the branched substitution product selectively (80%, 7:1 dr, and 99% ee, entry 9). Substituted 2-benzyl-1-tetralones also reacted to give products in 76−85% yield, 7:10:1 dr, 99% ee (entries 10−13). However, reactions with allyl-substituted allyl carbonates occurred with low diastereoselectivities.

The products of diastereo- and enantioselective allylic substitution reactions can be conveniently transformed into various polycarbocyclic compounds (Scheme 2). For example, the terminal double bond was readily converted to an aldehyde group in a one-pot dihydroxylation and cleavage of the resulting vicinal diol. The allylation product generated from 2-allyl-1-tetralone was converted to a spirocyclic product by ring-closing metathesis in the presence of the Grubbs−Hoveyda second-generation catalyst. The products lacking a second alkene can also be employed in a reaction sequence to produce fused polycyclic products. For example, an allylcerium reagent reacted efficiently (92% yield, 9:1 dr). Ring-closing metathesis of the resulting product yielded a product possessing a 6-7-6 tricyclic, fused ring system in 62% yield. This reaction sequence demonstrates an alternative to cycloaddition reactions to access enantioenriched compounds containing a seven-membered ring.

In summary, we have developed a set of diastereo- and enantioselective allylic substitution reactions of unstabilized, prochiral cyclic ketone enolates catalyzed by the phosphoramidite-ligated metallacyclic Ir complex. The stereoselectivity is achieved by combining phosphoramidite and barium enolates of ketones. The reactions provide rapid access to compounds containing vicinal quaternary and tertiary stereocenters diastereo- and enantioselectively. The products formed in this process can be readily transformed into various structural motifs, including spirocyclic compounds and fused polycyclic compounds.

The effects of the ligand and the enolate cation show that facial selectivity of prochiral nucleophiles leading to diastereo-selective allylations can be achieved, despite the lack of direct coordination of the ketone enolate to the metal center. Although the reactions we report are limited to those of cyclic

| Table 3. Ir-Catalyzed Allylic Substitutions of Allyl Carbonatesa,b |
|---|
| R | OCO2Me |
| 1 | OMe |
| 2 | Br |
| 3 | CF3 |
| 4 | F |
| 5 | Cl |
| 6 | N |
| 7 | OMe |
| 8 | OMe |
| 9 | OMe |
| 10 | Br |
| 11 | MeO |
| 12 | Br |
| 13 | MeO |

“See the SI for experimental details. Absolute configurations assigned by analogy; dr’s determined by 1H NMR analysis of the crude reaction mixtures; ee’s determined by chiral HPLC analysis.

Scheme 2. Transformation of the Allylation Products of Ketone Enolatesa

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the terminal double bond was readily converted to an aldehyde group in a one-pot dihydroxylation and cleavage of the resulting vicinal diol. The allylation product generated from 2-allyl-1-tetralone was converted to a spirocyclic product by ring-closing metathesis in the presence of the Grubbs−Hoveyda second-generation catalyst. The products lacking a second alkene can also be employed in a reaction sequence to produce fused polycyclic products. For example, an allylcerium reagent reacted with the allylation product of 2-benzyl-1-benzosuberone efficiently (92% yield, 9:1 dr). Ring-closing metathesis of the resulting product yielded a product possessing a 6-7-6 tricyclic, fused ring system in 62% yield. This reaction sequence demonstrates an alternative to cycloaddition reactions to access enantioenriched compounds containing a seven-membered ring.

In summary, we have developed a set of diastereo- and enantioselective allylic substitution reactions of unstabilized, prochiral cyclic ketone enolates catalyzed by the phosphoramidite-ligated metallacyclic Ir complex. The stereoselectivity is achieved by combining phosphoramidite 1b and barium enolates of ketones. The reactions provide rapid access to compounds containing vicinal quaternary and tertiary stereocenters diastereo- and enantioselectively. The products formed in this process can be readily transformed into various structural motifs, including spirocyclic compounds and fused polycyclic compounds.

The effects of the ligand and the enolate cation show that facial selectivity of prochiral nucleophiles leading to diastereo-selective allylations can be achieved, despite the lack of direct coordination of the ketone enolate to the metal center. Although the reactions we report are limited to those of cyclic
ketone enolates to form vicinal quaternary and tertiary stereocenters, the modularity of the phosphoramidite ligand and the ability to vary the composition of metal enolates could allow related reaction systems to effect diastereoselective reactions of a range of enolates derived from other ketones and carboxylic acid derivatives. Studies on stereoselective Ir-catalyzed alkylation reactions with acyclic ketone enolates are ongoing in this laboratory.

ASSOCIATED CONTENT

Supporting Information
Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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