Title

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Journal

Journal of the American Chemical Society, 136(45)

Authors

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Publication Date

2014-11-12

DOI

10.1021/ja506500u

Peer reviewed

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

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

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Supporting Information

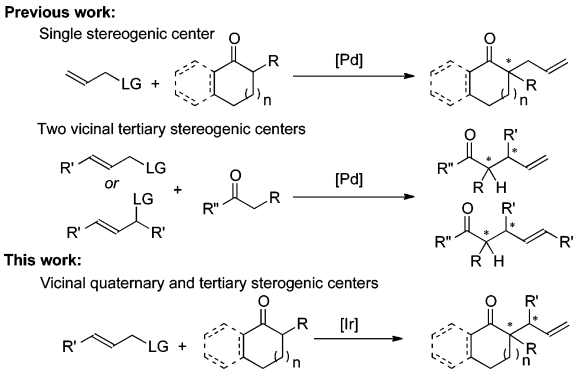
ABSTRACT: We report asymmetric allylic alkylation of barium enolates of cyclic ketones catalyzed by a metallacyclic iridium complex containing a phosphoramidite ligand derived from (*R*)-1-(2-naphthyl)ethylamine. The reaction products contain adjacent quaternary and tertiary stereocenters. This process demonstrates that unstabilized cyclic ketone enolates can undergo diastereo- and enantioselective Ir-catalyzed allylic substitution reactions with the proper choice of enolate countercation. The products of these reactions can be conveniently transformed to various useful polycarbocyclic structures.

Asymmetric alkylations of monocarbonyl compounds are commonly used to construct enantioenriched compounds, and many chiral auxiliaries and chiral reagents have been invented to effect such transformations.[1] Recent work has emphasized the discovery of catalytic asymmetric alkylation with transition metal catalysts,[2] Lewis acid catalysts,[3] phase-transfer catalysts,[4] and organic catalysts.[5] Palladium-catalyzed allylic substitution reactions have been a major focus of such efforts. Such reactions most commonly generate products containing a single stereocenter, although a few isolated examples have shown that products containing vicinal tertiary stereocenters were formed with good stereoselectivities (Scheme 1).[2g−j] However, methods to simultaneously form vicinal quaternary and tertiary stereocenters remain largely undeveloped.[6]

Enantioselective allylic substitution reactions catalyzed by metallacyclic iridium complexes have become a powerful tool to construct carbon−heteroatom[7] and carbon−carbon bonds.[8] Recently, our group, Carreira's group, and Stoltz's group have begun to show that Ir-catalyzed allylation reactions can be conducted to form products containing vicinal stereocenters with good to excellent diastereoselectivity and high enantioselectivity.[8g−l] Although these Ir-catalyzed reactions have started to address the challenge of conducting diastereoselective reactions of aldehydes or *β*-ketoesters as nucleophiles, diastereo- and enantioselective allylic alkylation of unstabilized prochiral ketone enolates remains challenging.

Previous mechanistic studies on Ir-catalyzed allylic substitution showed that the reaction occurs via a nucleophilic addition to the face of the allyl group opposite to the Ir moiety.[9] The crystal structure of the Ir-allyl complex shows that the Ir fragment completely blocks one face of the allyl group,[10] so the facial selectivity of prochiral nucleophiles dictates the diastereoselectivity of the reaction.

Scheme 1. Pd- and Ir-Catalyzed Allylation of Ketones



Here, we report Ir-catalyzed diastereo- and enantioselective allylation of a set of unstabilized cyclic ketone enolates to form products containing vicinal quaternary and tertiary stereogenic centers. This reactivity was achieved by combining barium enolates and a phosphoramidite ligand derived from (*R*)-1-(2-naphthyl)ethylamine. Subsequent transformations of the allylation products provide rapid access to enantioenriched polycarbocyclic compounds.

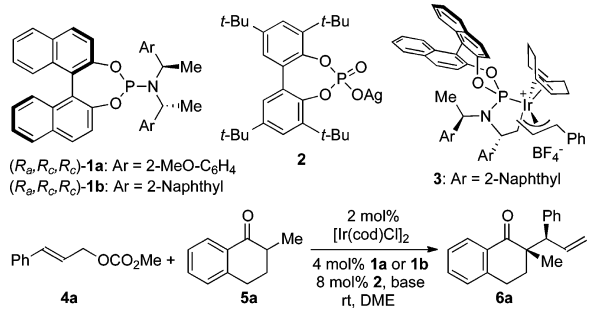
The reaction between methyl cinnamyl carbonate (**4a**) and 2-methyl-1-tetralone (**5a**) was investigated to evaluate the effects of the base and the ligand on reactivity and diastereoselectivity (Table 1). In the presence of $[Ir(cod)Cl]_2$, phosphoramidite **1a** and silver phosphate **2**, which led to diastereoselective reactions of azlactones,[8j] no reaction occurred between **4a** and **5a** in 1,2-dimethoxyethane (DME); presumably, the phosphate is not a sufficiently strong base to deprotonate the weakly 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.[11]

Because of the positive effect of magnesium enolates on the diastereoselectivity in the allylation of thiazolones,[8k] we studied systematically the effect of the alkaline earth metal on the

Received: June 27, 2014
Published: October 22, 2014

   dx.doi.org/10.1021/ja506500u | J. Am. Chem. Soc. 2014, 136, 15825−15828

Table 1. Effects of Ligand and Metal Enolates on the Ir-Catalyzed Allylation of 2-Methyl-1-tetralone[a]



entry	ligand	base	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	none	0		
2	**1a**	LHMDS	74	2.0:1	
3	**1b**	LHMDS	70	2.3:1	
4	**1a**	$Mg(Ot\text{-}Bu)_2$	10	1.1:1	
5	**1a**	$Ca(Oi\text{-}Pr)_2$	17	1.3:1	
6	**1a**	$Sr(Oi\text{-}Pr)_2$	64	1.7:1	
7	**1a**	$Ba(Ot\text{-}Bu)_2$	75	2.0:1	
8	**1b**	$Mg(Ot\text{-}Bu)_2$	15	1.6:1	
9	**1b**	$Ca(Oi\text{-}Pr)_2$	20	3.3:1	
10	**1b**	$Sr(Oi\text{-}Pr)_2$	61	4.5:1	
11	**1b**	$Ba(Ot\text{-}Bu)_2$	72	5.0:1	98
12[e]	**1b**	$Ba(Ot\text{-}Bu)_2$	83	9.0:1	98
13[e,f]	**1b**	$Ba(Ot\text{-}Bu)_2$	82 (81)	11.0:1	98
14[e,f,g]	**1b**	$Ba(Ot\text{-}Bu)_2$	83 (81)	11.0:1	98
15[h]	**1b**	$Ba(Ot\text{-}Bu)_2$	81	3.2:1	98

[a]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. [b]Determined by ^{1}H NMR analysis with mesitylene as the internal standard. Numbers in parentheses correspond to isolated yield. [c]Determined by ^{1}H NMR analysis of crude reaction mixtures. [d]Determined by chiral HPLC analysis of the major diastereomer. [e]THF instead of DME. [f]Reaction conducted at 5 °C. [g]2 mol% preformed catalyst **3** was used instead of the *in situ*-generated catalyst. [h]2.00 equiv of TMEDA was added under the same conditions as entry 14.

allylation of ketone enolates catalyzed by complexes generated from ligands **1a** and **1b** (entries 4−11).[12] Similar reactivities were observed in allylations of **5a** with catalysts derived from the two ligands. Although reactions conducted with $Mg(Ot\text{-}Bu)_2$ and $Ca(Oi\text{-}Pr)_2$ as the base gave the allylation product in low yields with a substantial amount of cinnamyl carbonate recovered, reactions conducted with $Sr(Oi\text{-}Pr)_2$ and $Ba(Ot\text{-}Bu)_2$ as the base afforded the allylation product in high yield.[13]

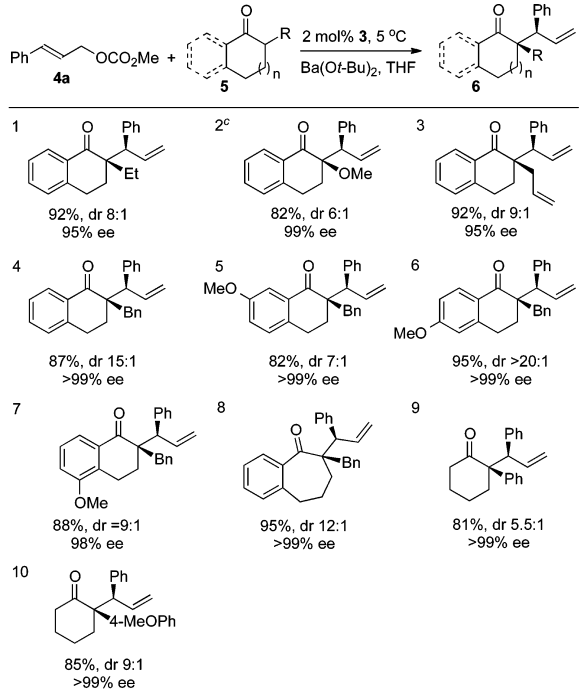
The effect of the two ligands on the diastereoselectivity, however, was distinct for reactions conducted with the Sr and Ba alkoxides. When barium enolates were employed as nucleophiles, the reaction conducted with the catalyst generated from ligand **1b** occurred with higher diastereoselectivity (entry 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.[14]

Table 2 summarizes the scope of the nucleophile in the allylation with Ba enolates and catalyst **3** under the conditions

Table 2. Ir-Catalyzed Allylation of Ketones[a,b]



[a]Both the enolates and the allylcarbonates were cooled to 5 °C prior to mixing. See the SI for experimental details. [b]Absolute configurations were assigned by analogy; dr's were determined by ^{1}H NMR analysis of the crude reaction mixtures; ee's determined by chiral HPLC analysis. [c]*tert*-Butyl cinnamylcarbonate as the substrate.

described above. All of these reactions provided the branched product **6** exclusively. The reactions of 2-substituted tetralones occurred smoothly to give the products in high yield and good diastereoselectivity with excellent enantioselectivity (entries 1−4). Reactions of tetralones **5** with substituents at various positions on the phenyl ring were also examined. Allylation of these tetralones gave products in 82−95% yield, 7−20:1 dr, and 98−99% ee (entries 5−7).

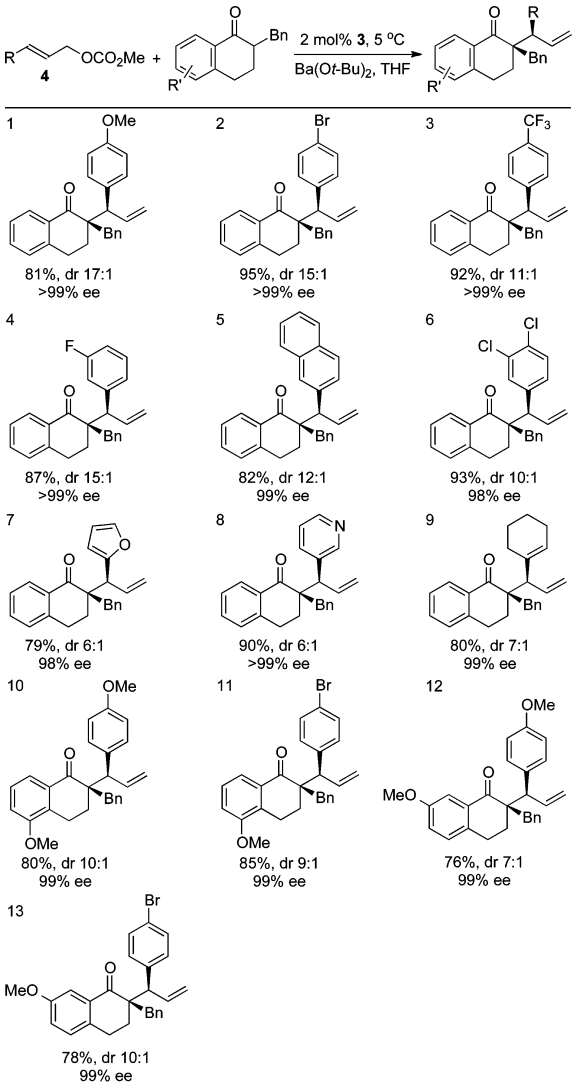
In addition to the reactions of 1-tetralone derivatives, reactions of other benzene-fused cycloalkanones and cyclohexanone derivatives were studied. 2-Benzyl-1-benzosuberone underwent the allylation reaction to form the product in 95%

dx.doi.org/10.1021/ja506500u | J. Am. Chem. Soc. 2014, 136, 15825−15828

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 **4** 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).

Table 3. Ir-Catalyzed Allylic Substitutions of Allyl Carbonates[a,b]

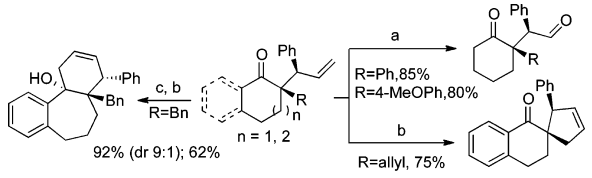


[a]See the SI for experimental details. [b]Absolute configurations assigned by analogy; dr's determined by ^{1}H NMR analysis of the crude reaction mixtures; ee's determined by chiral HPLC analysis.

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 alkyl-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 with the allylation product of 2-benzyl-1-benzosuberone efficiently (92% yield, 9:1 dr).[15] 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.

Scheme 2. Transformation of the Allylation Products of Ketone Enolates[a]



[a]Conditions: (a) 5 mol% OsO_4, $NaIO_4$, ether/H_2O, rt. (b) Grubbs–Hoveyda second-generation catalyst, DCM, 40 °C. (c) AllylMgBr, $CeCl_3$, THF, rt.

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 diastereoselective allylations can be achieved, despite the lack of direct coordination of the ketone enolate to the metal center.[9,10,16] Although the reactions we report are limited to those of cyclic

dx.doi.org/10.1021/ja506500u | J. Am. Chem. Soc. 2014, 136, 15825–15828

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 allylation 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.

■ ACKNOWLEDGMENTS

We thank the NIH (GM-58108) for support of methods development, the Director, Office of Science, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231 for support of our studies on effects of the outer coordination sphere, NIH Shared Instrumentation Grant (S10-RR027172) for support of Berkeley X-ray crystallography, Johnson-Matthey for gifts of $[Ir(cod)Cl]_2$, and Dr. Klaus Ditrich and BASF for a generous gift of chiral amines.

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(13) Isopropoxide and *tert*-butoxide appeared to work similarly and effectively suppressed undesired O-allylation reactions.

(14) See the SI for the details of the conditions screened, including vaious alkoxide and amide bases, solvents, and additives.

(15) The absolute stereochemistry of the product was established through X-ray analysis. See the SI for the details.

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