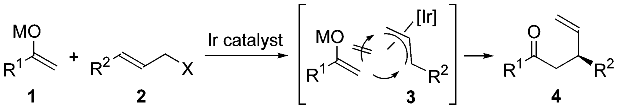
J|A|C|S
COMMUNICATIONS

Iridium-Catalyzed Regio- and Enantioselective Allylation of Ketone Enolates

Timm Graening and John F. Hartwig*
Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

Received September 27, 2005; E-mail: john.hartwig@yale.edu

Enantioselective allylic alkylation of ketone enolates is much less developed than the enantioselective additions of more stabilized nucleophiles derived from 1,3-dicarbonyl compounds.[1] Enantioselective additions of ketone enolates to the less-hindered position of allyl electrophiles, as well as to symmetrically substituted allyl electrophiles, are known,[2] but enantioselective reactions of unstabilized enolates that form chiral, branched substitution products from unsymmetrical allylic electrophiles (eq 1)[3] have not been reported. Moreover, the formation of the same products by a more classical aliphatic Claisen rearrangement has not yet been accomplished as a catalytic enantioselective process.



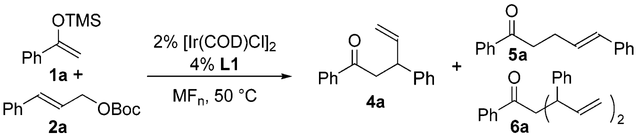
(1)

The metal-catalyzed asymmetric allylation of unstabilized ketone enolates is challenging because the nucleophile must preferentially attack the π-allyl intermediate over the carbonyl group of the product, the ketone product must resist re-formation of an enolate followed by reaction with a second allyl electrophile, and reactions of monosubstituted allylic substrates must occur regioselectively at the more substituted terminus of an allyl intermediate. We have now found that reactions of allylic carbonates with silyl enol ethers and a combination of CsF and ZnF_2 additives catalyzed by metallacyclic iridium phosphoramidite complexes meet these challenges, and we report reactions of these enolates with achiral allylic carbonates to form chiral, branched homoallylic ketones with high regio- and enantioselectivity.

To develop additions of silyl enol ethers with allylic electrophiles, we began by studying reactions catalyzed by metallacyclic iridium complexes that we have shown to catalyze allylic amination and etherification.[4] These catalysts are formed by combining $[Ir(COD)Cl]_2$ with particular phosphoramidite ligands and heating with an amine to induce cyclometalation.[5] Reactions of silyl enol ethers alone did not form any allylation product. However, reactions containing a series of metal fluorides revealed that the silyl enol ether **1a** derived from acetophenone reacted with *tert*-butyl cinnamyl carbonate (**2a**) in the presence of CsF.[6] Although the reactions with CsF occurred with modest selectivity (entry 2, Table 1), the reactions with a *combination* of ZnF_2 and CsF occurred with much higher selectivity (entries 3−5 of Table 1). No reaction occurred when only ZnF_2 was added (entry 1, Table 1).

Reactions with substoichiometric amounts of CsF formed little of the diallylation product. Although the reactions with only 0.05 equiv of CsF required 3 days (entry 4), reactions with a ratio of enolate **1a** to CsF to ZnF_2 of 1.2:0.2:1.2 occurred to completion within 18 h, with a high branched-to-linear regioselectivity (93:7) and without formation of amounts of diallylation product detectable by ^1H NMR spectroscopy (entry 5). Because the activated, cyclometalated catalyst could also be generated in situ (vide infra), reactions also occurred without preactivation of the catalyst, and these reactions went to completion with a ratio of **1a** to CsF to ZnF_2 of 1.5:0.4:1.5 in pure DME (entry 6). At this point, it remains uncertain whether a cesium, zinc, or hypervalent silicon enolate is the reactive nucleophile in these reactions.

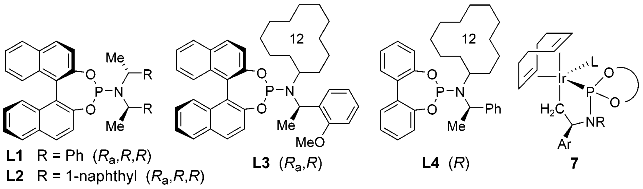
Table 1. Effect of CsF and ZnF_2 on the Ir-Catalyzed Allylation of Acetophenone Silyl Enol Ether **1a**[a]



entry	molar ratios relative to **2a**: **1a**	CsF	ZnF_2	*t* (h)	% conv.[b]	ratio[b] **4a:5a:6a**
1[c]	1.2	−	1.2	24	0	−
2[c]	1.2	1.2	−	24	100	60:17:23
3[d]	1.5	1.5	1.5	24	100	78:8:14
4[d]	1.2	0.05	1.2	72	75	87:11:2
5[d]	1.2	0.2	1.2	18	100	92:7:<1
6[c]	1.5	0.4	1.5	8	100	97:2:<1

[a] Reaction conditions: 1 mmol **2a** (0.6 M), 4 mol % of **L1**, and 2 mol % of $[Ir(COD)Cl]_2$, 50 °C. [b] The conversion of **2a** and the ratio of the products were determined from ^1H NMR spectra of the crude reaction mixtures. [c] DME was the solvent. [d] The catalyst was activated by treatment with propylamine prior to the reaction, and THF/diglyme (2:1) was the solvent.

Table 2. Comparison of Selected Ligands for the Ir-Catalyzed Allylation of Silyl Enol Ether **1a** with Cinnamyl Carbonate **2a**[a]



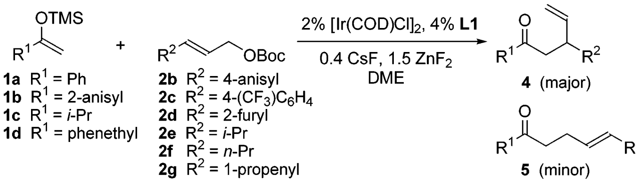
entry	ligand	% yield	branched/linear[b]	% *ee* (abs. config.)[c]
1	**L1**	84	93:7	94 (*R*)
2	**L2**	86	96:4	91 (*R*)
3	**L3**	89	92:8	95 (*R*)
4	**L4**	70[d]	95:5	92 (*R*)

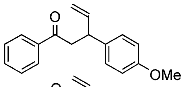
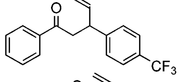
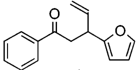
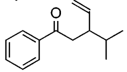
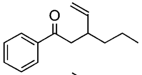
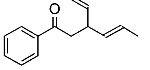
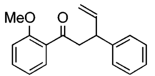
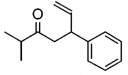
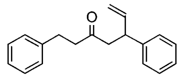
[a] Reactions were conducted under the conditions of entry 5, Table 1. [b] The branched-to-linear ratio was determined by ^1H NMR spectroscopy of the crude reaction mixtures. [c] Enantiomeric excesses were determined by HPLC using a Daicel Chiralcel OD-H column with hexanes/2-propanol (99:1) as the eluent. [d] After 94% conversion.

Table 2 shows that the more elaborate (**L1**, **L2**)[7] as well as the stereochemically simpler (**L3**, **L4**) phosphoramidite ligands developed recently by our group for iridium-catalyzed allylic amination and etherification[8] catalyzed the allylation of silyl enol ethers in high yield. Each of these ligands has been shown to generate metallacycles with the general structure **7** shown above Table 2.[5,8] Reactions of silyl enol ethers catalyzed by complexes generated from ligands **L1** and **L2** occurred with high levels of enantioselectivity and regioselectivity. Reactions catalyzed by the stereochemically simpler ligand **L3** (entry 3) occurred with nearly as high a regioselectivity (92:8) and in higher enantioselectivity (95%), while reactions catalyzed by the ligand **L4** (entry 4) possessing

10.1021/ja0566275 CCC: $30.25 © 2005 American Chemical Society

Table 3. Iridium-Catalyzed Allylation of Silyl Enol Ethers[a]



entry	substrates	product structure	*t* [h]	% yield[b]	**4** : **5**[c]	% *ee*[d]
1	**1a**, **2b**		6	94	99 : 1	96
2	**1a**, **2c**		12	81	94 : 6	95
3	**1a**, **2d**		16	74	99 : 1	96
4	**1a**, **2e**		40	75[e]	85 : 15	94
5	**1a**, **2f**		8	92[e]	87 : 13	92
6	**1a**, **2g**		18	85	95 : 5	95
7	**1b**, **2a**		18	62	98 : 2	96
8	**1c**, **2a**		40	46	95 : 5	91
9	**1d**, **2a**		18	54	99 : 1	94

[a] Reactions were conducted under the conditions of entry 6, Table 1. [b] Average isolated yields of two independent runs. [c] The ratio of branched and linear isomers (**4**:**5**) was determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Enantiomeric excesses were determined by HPLC on chiral stationary phases for reactions with both enantiomers of **L1**. [e] Combined yields for isomers **4** and **5**.

only one resolved stereocenter occurred with high branched-to-linear ratio (95:5), as well as high enantiomeric excess (92%).

Table 3 summarizes the scope of the Ir-catalyzed allylation of silyl enol ethers in the presence of CsF and ZnF_2 catalyzed by the combination of $[Ir(COD)Cl]_2$ and **L1** under the conditions of entry 6, Table 1. *tert*-Butyl carbonates derived from γ-arylallyl alcohols formed products with benzylic stereocenters with high regio- and enantioselectivity (entries 1−3). The electron-rich, 4-methoxy cinnamyl carbonate **2b** reacted in the highest yield, branched-to-linear ratio, and enantiomeric excess, but the electron-poor, 4-trifluoromethyl-substituted cinnamyl carbonate **2c** reacted with only slightly lower regioselectivity and essentially identical enantiomeric excess. The reactions of 2-furyl-substituted allylic carbonate **2d** occurred with the same high selectivity as reactions of carbonate **2b**. Reactions of the aliphatic carbonates **2e** and **2f** (entries 4 and 5) also occurred in high yield and enantiomeric excess, although the regioselectivity was lower (85:15 to 87:13). Reaction of the dienyl carbonate **2g** (entry 6) occurred with selectivities akin to those of the aromatic substrates.

Silyl enol ethers beyond those derived from acetophenone also underwent the allylation process (entries 7−9). 2-Anisyl derivative **1b** reacted with excellent selectivity, and even aliphatic silyl enol ethers **1c** and **1d** reacted with good to nearly perfect regioselectivity, although in lower yields. The lower yields from reactions of **1c** and **1d** could have resulted from formation of enolate regioisomers, but no major additional allylated side product was detected in the ^{1}H NMR spectra of the crude reaction mixtures.

The absolute configuration of the reaction product **4a** was determined to be (*R*) by comparison of the specific rotation of the product after hydrogenation with literature data. The stereochemistry of these reactions parallels the stereochemistry of the reactions of softer malonate[9] and amine nucleophiles[10] in the presence of the same Ir catalysts.

^{31}P NMR spectroscopic studies of the reaction showed that the enolates and fluoride additives lead to the metallacyclic iridium catalyst (**7**) derived from **L1**, even without initial treatment of [Ir(COD)(**L1**)Cl] with base. The initial singlet resonance at $\delta = 116.4$ ppm due to the square planar [Ir(COD)(**L1**)Cl] at the start of reactions catalyzed by 2 mol % of $[Ir(COD)Cl]_2$ and 4 mol % of **L1** in DME was replaced after 4 h and approximately 40% conversion by two doublets ($\delta = 128.8$ and 154.1 ppm, $^3J_{P,P} = 44.6$ Hz) corresponding to the iridacycle **7** bearing one κ^2, P,C-bound **L1** and one κ^1, P-bound **L1**.[5]

Thus, we have developed conditions for enantioselective α-allylation of unstabilized ketone enolates catalyzed by metals other than palladium and enantioselective α-allylation of unstabilized ketone enolates that form branched isomers as the major product. These reactions appear to occur through an iridacyclic catalyst. By this reaction, bifunctional γ,δ-unsaturated ketones are prepared in optically active form from readily available silyl enol ethers and Boc-protected allylic alcohols. Although the products of the reactions in this study are available, in principle, by Claisen rearrangement, none of the products in Table 3 had been prepared previously in optically active form.

Acknowledgment. We thank the NIH (NIGMS-58108) for support. T.G. thanks the DFG for a postdoctoral fellowship. We thank Dr. Chutian Shu for initial experiments with Zn enolates.

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

References

(1) (a) Negishi, E.-I.; Liou, S.-Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley: New York, 2002; Vol. 2, p 1769. For enantioselective additions of malonate-type nucleophiles to the more substituted terminus of allylic substrates, using metals other than palladium, see: (b) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (c) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141. (d) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. (e) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. (f) Fuji, K.; Kinoshita, N.; Tanaka, K.; Kawabata, T. *Chem. Commun.* **1999**, 2289.

(2) (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3494. (c) You, S.; Hou, X.; Dai, L.; Zhu, X. *Org. Lett.* **2001**, *3*, 149. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (e) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (f) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (g) Yan, X.; Liang, C.; Zhang, Y.; Hong, W.; Cao, B.; Dai, L.; Hou, X. *Angew. Chem., Int. Ed.* **2005**, ASAP.

(3) For examples of stereospecific reactions with achiral Ru and Rh catalysts, see: (a) Burger, E. C.; Tunge, J. A. *Chem. Commun.* **2005**, 2835. (b) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974.

(4) (a) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (b) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093.

(5) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272.

(6) For the use of similar promoters in the α-arylation of silyl ketene acetals and α-silyl nitriles, see: (a) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182. (b) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(7) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.

(8) (a) Leitner, A.; Shu, C.; Hartwig, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5830. (b) Leitner, A.; Shekhar, S.; Pouy, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506.

(9) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569.

(10) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.

JA0566275