J|A|C|S
COMMUNICATIONS

Published on Web 06/02/2007

Regioselective and Enantioselective Iridium-Catalyzed Allylation of Enamines

Daniel J. Weix and John F. Hartwig*

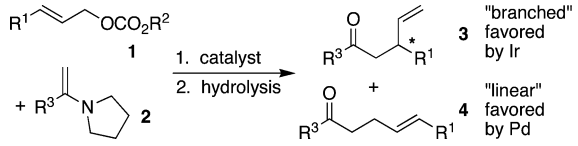
Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520, and Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801

Received March 1, 2007; E-mail: jhartwig@uiuc.edu

We report highly enantioselective allylations of enamines that occur with high regioselectivity for addition at the branched position of allyl electrophiles. Conventionally, the asymmetric synthesis of these allylated ketones has been conducted with β-ketoesters and requires a separate decarboxylation step. The allylations of enamines address the challenge of conducting enantioselective allylation of so-called unstabilized enolates, particularly reactions of both aromatic and aliphatic acyclic ketones.[1] Such reactions were reported with palladium catalysts many years ago, but little enantioselective allylation of these classic nucleophiles has been reported.[2] Moreover, no allylations of enamines catalyzed by complexes that control the stereochemistry at the electrophile have been reported.

As shown in Scheme 1, palladium catalysts for the allylation of enamines with monosubstituted allyl electrophiles are known to form the linear substitution products.[1] We show that the analogous reactions of enamines in the presence of a metalacyclic iridium catalyst form the branched product[3] with high enantioselectivity and regioselectivity with a range of allyl electrophiles, in the absence of added base,[1,4] without activators,[5] and without the need to prepare substituted enol carbonates.[1,6] These reactions of enamines occur in good yields with both aliphatic and aromatic ketones, and they occur with high selectivity for the monoallylation of unhindered methyl ketones.

Scheme 1



The development of conditions to conduct the enantioselective allylation of enamines relied on the use of a preformed iridium catalyst containing a cyclometalated phosphoramidite ligand, the appropriate enamine, an aromatic solvent, and an additive to adsorb the alcohol product. Previous work from our laboratories has shown that iridium phosphoramidite catalysts for allylic substitution become active by cyclometalation of the ligand with a basic reagent to form the structure **5** in Figure 1.[7] This cyclometalated catalyst was used in our labs[8] and subsequently by others[9] for the allylation of amines, alcohols, phenols, silanolates, and activated methylene compounds. Because enamines are not sufficiently basic to induce the cyclometalation process, we studied reactions of enamines using a cyclometalated catalyst **5** that was generated by heating of phosphoramidite **L1** (Figure 1) with $[Ir(cod)Cl]_2$ at 50 °C for 1 h in the presence of propylamine.[7] Our studies focused on reactions of pyrrolidine enamines because their nucleophilicity is greater than that of other standard enamines, such as morpholine enamines.

Initial reactions of the pyrrolidine enamine of acetophenone (**2a**) with methyl cinnamyl carbonate in the presence of the iridium catalyst **5** formed the branched substitution product with no detectable diallylation products. However, the allylation of enamines occurred in competition with allylation of free pyrrolidine, presumably formed by decomposition of the enamine in the presence of $PrNH_3Cl$ generated during the catalyst activation. This allylation of pyrrolidine was suppressed by conducting the reaction in the presence of 5 Å molecular sieves. As shown in Scheme 2, the branched-to-linear (b:l) ratios and enantioselectivities of the reactions of aromatic and aliphatic enamines **2a** and **2b** conducted with 5 Å MS were high. However, the reactions were slow, even when conducted with 5 mol % of Ir. Furthermore, aliphatic carbonates did not react under these conditions.

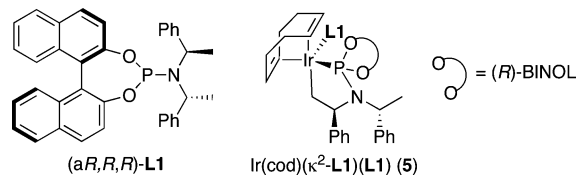
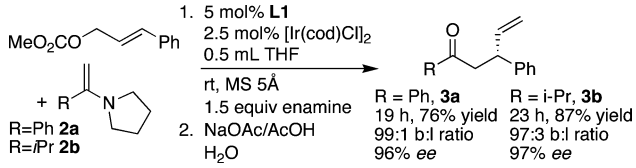


Figure 1. Phosphoramidite ligand **L1** and structure of cyclometalated five-coordinate Ir catalyst precursor Ir(cod)(κ^2-**L1**)(**L1**), **5**.

Scheme 2

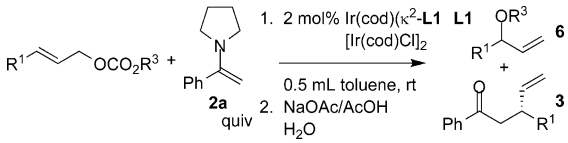


A change in solvent, the use of pure, isolated cyclometalated complex **5** in combination with $[Ir(cod)Cl]_2$,[7] and the use of isopropyl carbonates led to increased rates and successful reactions with aliphatic carbonates. The b:l ratios were high from reactions of cinnamyl methyl carbonate and enamine **2a** in all solvents in the presence of the unpurified, cyclometalated catalyst, but enantioselectivities were lower in more polar solvents: THF, EtOAc, toluene (95−96% ee) > NMP (84% ee) > CH_2Cl_2 (82% ee) > DMF, MeCN (77−80% ee). Lower enantioselectivities from reactions in more polar solvents have been observed previously with this catalyst.[10] Reactions in toluene occurred with the best balance of rate and selectivity.

The use of the isolated catalyst **5** (Table 1) led to the fastest reactions of cinnamyl carbonate and reactions with aliphatic carbonates. Reactions of different carbonates with a series of additives are summarized in Table 1. The reaction of methyl cinnamyl carbonate with the enamine **2a** under these conditions occurred in only 2 h without the formation of the products from allylation of pyrrolidine but with competitive formation of products from decarboxylative etherification of the allylic carbonate (**6** in Table 1). The formation of products from internal collapse of the allylic carbonate was suppressed by conducting reactions with the more hindered isopropyl carbonates (Table 1, entries 2−5) and by the addition of $CaCl_2$ or $ZnCl_2$ to trap the released isopropanol. $CaCl_2$ and $ZnCl_2$ were tested because they are known to form alcoholates with high binding energies.[11] Reactions with added

10.1021/ja071455s CCC: $37.00

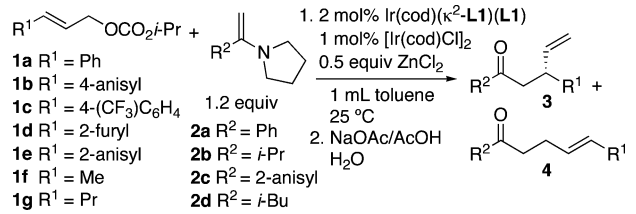
Table 1. Effect of Leaving Group and Additives[a]



entry	R^1	OCO_2R_3	*t* (h)	additive	yield[b] **3** (%)	yield[b] **6** (%)
1	Ph	OCO_2Me	2	5 Å MS	85	17
2		OCO_2Et	1.5	5 Å MS	88	8
3		OCO_2i-Bu	1.5	5 Å MS	78	15
4		OCO_2i-Pr	2.5	5 Å MS	94	4
5		OCO_2t-Bu	6	5 Å MS	91	<2
6	Me	OCO_2i-Pr	21	none	28	nd[c]
7		OCO_2i-Pr	21	$CaCl_2$	59	nd[c]
8		OCO_2i-Pr	21	$ZnCl_2$	66	nd[c]

[a] See Supporting Information. [b] NMR yield. [c] Byproduct **6** is volatile.

Table 2. Ir-Catalyzed Allylation of Enamines[a]



entry	R^1	R^2	**3**	*t* (h)	yield[b] (%)	**3**:**4**[c]	% ee[d]
1	Ph	Ph	**3a**	6	91	>99:1	94
2	Ph	*i*-Pr[e]	**3b**	5	86	>99:1	95
3	Ph	2-anisyl	**3c**	3.5	86	96:4	96
4[f]	Ph	*i*-Bu[g]	**3d**	4	91	98:2	96
5[h]	4-anisyl	*i*-Bu[g]	**3e**	2	91	97:3	96
6[h]	4-$(CF_3)C_6H_4$	*i*-Bu[g]	**3f**	11	75	85:15	94
7[h]	2-furyl	*i*-Bu[g]	**3g**	2	90	98:2	97
8[h]	2-anisyl	*i*-Bu[g]	**3h**	7.5	86	98:2	77
9[h,i]	Me	Ph	**3i**	4	68	95:5	94
10[j]	Pr	*i*-Bu[g]	**3j**	39	64	89:11	83
11[k]	Ph	*i*-Bu[g]	**3d**	11	84	98:2	95

[a] See Supporting Information. [b] Isolated yield of **3**. [c] Determined by NMR and/or GC/MS. [d] Determined by HPLC. [e] 95:5 ratio of regioisomers. [f] Average of three runs. [g] 68:32 ratio of regioisomers. [h] Average of two runs. [i] 2 equiv of enamine. [j] 1.5 equiv of enamine, 35 °C. [k] Reaction run with 0.5 mol % of Ir(cod)(κ²-**L1**)(**L1**) and 0.25 mol % of $[Ir(cod)Cl]_2$.

$ZnCl_2$ occurred in slightly higher yield than reactions with added $CaCl_2$ (Table 1, entries 7 and 8).

The reactions of a variety of enamines (**2a**−**d**) with allylic carbonates (**1a**−**g**) were conducted under these optimized conditions (Table 2). While reactions were nearly complete in as little as 1 h (entry 5), reactions were allowed to run for several hours. Reaction rates were similar for reactions of different enamines (entries 1−4), but varied with the electronic (entries 4−7) and steric (entries 5 vs 8 and 9 vs 10) properties of the allylic carbonate.[12]

The regioselectivities at the allyl and enamine units were high in most cases. The reaction of the electron-poor, *p*-CF_3-substituted cinnamyl carbonate **1c** with the enamine of isobutyl methyl ketone (**2d**) and the reaction of hexenyl carbonate **1g** with enamine **2d** occurred with b:l ratios of 85:15 (entry 6) and 89:11 (entry 10). All other reactions occurred with b:l ratios greater than 95:5. The reactions of enamines from methyl alkyl ketones that exist as mixtures of two regioisomers occurred regioselectively (≥99:1) at the less hindered position. The enantioselectivities were also high in most cases. All reactions occurred in ≥94% ee, except for that of enamine **2d** with *o*-methoxycinnamyl 2-propyl carbonate (**1e**)[10] (77% ee) and that of **2d** with hexenyl carbonate **1g** (83% ee). In addition, the fast rates allowed carbonate **1a** to react with enamine **2d** in the presence of 1 mol % of total iridium (0.5 mol % of [Ir(cod)(κ²-**L1**)(**L1**)] and 0.25 mol % of $Ir(cod)Cl]_2$) without any significant change in yield, b:l ratio, or enantioselectivity (entry 11).

Published iridium-catalyzed allylations of aliphatic silyl enol ethers occurred in only 46−54% yield, and reaction times were also long (18−40 h).[5] In contrast, the allylations of aliphatic enamines generally occurred in high yield, with high selectivity, and with much shorter reaction times (Table 2, entries 2, 4−8, and 11). The aliphatic enamine (**2d**) even coupled with a generally less reactive straight chain allylic carbonate (**1g**) in satisfactory yield and ee at 35 °C (entry 10).[12] The allylation of aliphatic ketones with allylic esters containing aliphatic substituents is rare.[1a,6c]

In summary, we have developed the first catalytic enantioselective allylation of ketone enamines to give the products from addition to the more substituted position of an allyl electrophile, and these reactions encompass rare examples of the enantioselective allylation of any acyclic aliphatic ketone.[1,13] Notable features of these reactions include the absence of diallylation products, regioselective allylation at the less hindered position of the enamine, high yields from reactions of aliphatic ketone enamines, and high enantioselectivities with a broad range of enamine nucleophiles and carbonate electrophiles. Studies to extend these methods to the reactions of prochiral enamines, aldehyde enamines, and 1,1-bis(amino)ethylenes are ongoing.

Acknowledgment. We acknowledge financial support from the NIH (NIH-GM58108 to J.F.H. and GM075703 to D.J.W.) and a gift of $IrCl_3$ from Johnson-Matthey. We thank Mark Pouy, Dr. Timm Graening, and Dr. Yasuhiro Yamashita for synthesis of several allylic alcohols used in this work. We thank the Denmark and Zimmerman groups for the use of their instruments.

Supporting Information Available: Detailed experimental procedures and spectral data for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952. (b) Braun, M.; Meier, T. *Synlett* **2006**, 661. (c) Negishi, E.-i.; Liou, S.-y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 2, p 1769.
(2) Using chiral auxilliaries: (a) Hiroi, K.; Abe, J.; Suya, K.; Sato, S.; Koyama, T. *J. Org. Chem.* **1994**, *59*, 203. Using enantioselective catalysis: (b) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952. See Supporting Information for data.
(3) Constant, S.; Tortoioli, S.; Müller, J.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2082.
(4) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.
(5) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192.
(6) (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (b) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (c) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, *2005*, 1715.
(7) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272.
(8) (a) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770. (b) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506.
(9) (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 674. (b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349. (c) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596. (d) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204. (e) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774.
(10) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.
(11) (a) Carling, R. W.; Wondolowski, A. T.; Macmillan, D. C. *J. Chem. Thermodyn.* **1982**, *14*, 125. (b) Hopfinger, C. M. *Am. Midland Nat.* **1912**, *2*, 249.
(12) Thus far, reactions of the more hindered aliphatic allylic carbonate with branching α to the allyl group (R^1 = *i*-Pr) have occurred to low conversions.
(13) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544.

JA071455S