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# Ir-Catalyzed Regio- and Enantioselective Decarboxylative Allylic Alkylations

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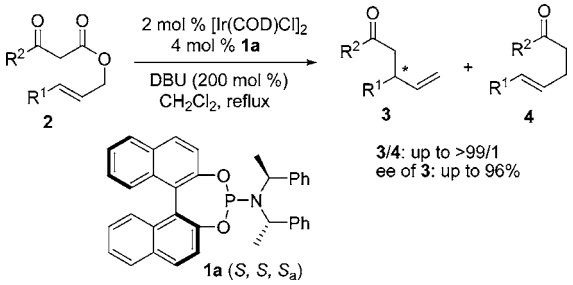
## ABSTRACT




**[Ir(COD)Cl]$_2$/phosphoramidite ligand 1a was found to be an efficient catalytic system for the highly regio- and enantioselective decarboxylative alkylation of $\gamma$-substituted allyl $\beta$-ketocarboxylates, affording the branched products with up to >99/1 branched-linear ratio and 96% ee.**

Transition-metal-catalyzed asymmetric allylic alkylation (AAA) has become one of the most efficient ways to construct carbon−carbon bonds with stereocenters.[1] Although high enantioselectivities could be achieved with soft nucleophiles and symmetrical allylic substrates, particularly, with a palladium catalyst, enantioselectivity with ketone enolates as nucleophiles[2] and regioselectivity related to unsymmetrical allylic substrates[3] remain challenging. Recently, Hartwig and co-workers reported the Ir-catalyzed highly regio- and enantioselective allylations of silyl enol ethers or enamines to tackle both of the problems.[4] As high enantioselectivities were obtained for palladium-catalyzed decarboxylative allylic alkylations involving ketone enolates generated in situ,[5−7] we envisaged that highly regio- and enantioselective allylation of ketone enolates might be achieved through decarboxylative allylic alkylation of allyl $\beta$-ketocarboxylates in

(1) Reviews: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(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.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149. (d) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2005**, *11*, 174. (e) 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. (f) Bélanger, E.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034. For review: (g) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952.

(3) (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (c) Hou, X.-L.; Sun, N. *Org. Lett.* **2004**, *6*, 4399. (d) Pamies, O.; Dieguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. (e) Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151. (f) Faller, J. W.; Wilt, J. C. *Organometallics* **2005**, *24*, 5076. (g) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61. (h) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718.

(4) (a) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192. (b) Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720.

(5) For reviews: (a) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, *9*, 1715. (b) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246.

(6) For recent examples: (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (b) Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun.* **2005**, 3951. (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (e) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (f) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248. (g) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109. (h) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (i) Schulz, S. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3966. (j) Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4077.

(7) For a Ru-catalyzed enantioselective Carroll rearrangement, please see: Constant, S.; Tortoioli, S.; Müller, J.; Lacour, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2082.

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the presence of an Ir catalyst,[8] known to give branched product for unsymmetrical allylic substrates (Figure 1).[9,10]

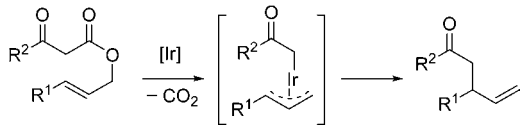
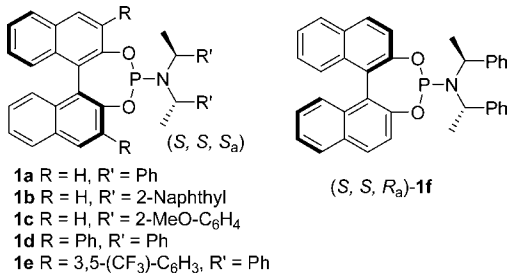



**Figure 1.** Ir-catalyzed decarboxylative allylic alkylation with unsymmetrical allylic substrates.

In this paper, we report our preliminary results on Ir-catalyzed highly regio- and enantioselective decarboxylative alkylation of $\gamma$-substituted allyl $\beta$-ketocarboxylates.

We began our studies with a well-developed Ir catalytic system including $[Ir(COD)Cl]_2$ and a phosphoramidite **1a** (Figure 2) as the catalyst.[11]




**1a** R = H, R' = Ph
**1b** R = H, R' = 2-Naphthyl
**1c** R = H, R' = 2-MeO-$C_6H_4$
**1d** R = Ph, R' = Ph
**1e** R = 3,5-$(CF_3)$-$C_6H_3$, R' = Ph

**Figure 2.** BINOL-derived phosphoramidite ligands **1a**−**f**.

In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, and 2 equiv of DBU, allyl $\beta$-ketocarboxylate **2a** smoothly underwent the decarboxylative alkylation in boiling $Et_2O$, affording 99/1 regioselectivity in favor of branched product **3a** with 95% ee (entry 1, Table 1). As summarized in Table 1, several conventional solvents and different reaction temperatures were tested. The reaction proceeded well from room temperature in $CH_2Cl_2$ to 75 °C in DME or toluene,

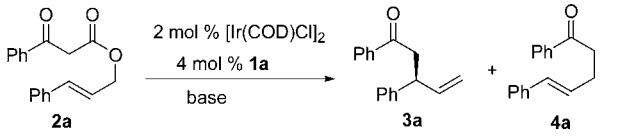
(8) During the course of our study, an excellent report on Ir-catalyzed regio- and enantioselective decarboxylative allylic amination appeared: Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774.

(9) For reviews: (a) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641. (b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349. (c) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun*. **2007**, 675.

(10) For recent examples: (a) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426. (b) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc*. **2003**, *125*, 14272. (c) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506. (d) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596. (e) Schelwies, M.; Dübon, P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2466. (f) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707. (g) Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546. (h) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204. (i) Nemoto, T.; Sakamoto, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 8737. (j) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.

(11) The catalyst was preformed in the presence of propylamine as described in ref 10c.

**Table 1.** Optimization of the Reaction Conditions for Ir-Catalyzed Decarboxylative Allylic Alkylation with Ligand **1a**[a]




| entry | solvent | base | time (h) | temp | yield[b] (%) | 3a/4a[c] | ee[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | $Et_2O$ | DBU | 16 | reflux | 66 | 99:1 | 95 |
| 2 | THF | DBU | 16 | reflux | 80 | 99:1 | 94 |
| 3 | DME | DBU | 16 | 75 °C | 75 | 98:2 | 94 |
| 4 | toluene | DBU | 16 | 75 °C | 61 | 98:2 | 85 |
| 5 | $CH_2Cl_2$ | DBU | 20 | 25 °C | 67 | >99:1 | 96 |
| 6 | $CH_2Cl_2$ | DBU | 16 | reflux | 83 | 99:1 | 95 |
| 7 | $CH_2Cl_2$ | none | 24 | reflux | 41 | >99:1 | 84 |
| 8 | $CH_2Cl_2$ | BSA/KOAc | 24 | reflux | 54 | 99:1 | 94 |
| 9 | $CH_2Cl_2$ | DBN | 8 | reflux | 75 | 99:1 | 94 |
| 10 | $CH_2Cl_2$ | DABCO | 8 | reflux | 80 | 99:1 | 94 |
| 11 | $CH_2Cl_2$ | $Cs_2CO_3$ | 18 | reflux | 62 | 99:1 | 93 |
| 12 | $CH_2Cl_2$ | KOAc | 23 | reflux | 73 | 99:1 | 93 |
| 13 | $CH_2Cl_2$ | $Et_3N$ | 22 | reflux | 84 | 98:2 | 93 |
| 14 | $CH_2Cl_2$ | $K_2CO_3$ | 24 | reflux | 62 | 99:1 | 92 |

[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, 0.2 mmol of **2a**, 0.4 mmol of base in 2 mL of solvent. [b] Isolated yields. [c] Determined by $^1H$ NMR after a short silica gel column. [d] Determined by chiral HPLC analysis (Chiralcel OD-H).

affording **3a** with excellent enantiomeric excesses (entries 3−5, Table 1). Running the reaction in refluxing $CH_2Cl_2$ led to a good combination of yield and selectivity (83% yield, **3a**/**4a**: 99/1, ee of **3a**: 95%, entry 6, Table 1). Interestingly, reaction without DBU resulted in a decrease of both yield and enantioselectivity of **3a** (entry 7, Table 1). Various organic and inorganic bases are also suitable for this transformation but show no beneficial effect over that of DBU (entries 8−14, Table 1).

Next we examined the effects of different phosphoramidite ligands, and the results are summarized in Table 2. Ligands

**Table 2.** Screening of the Phosphoramidite Ligands[a]

| entry | ligand | time (h) | yield[b] (%) | 3a/4a[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | 16 | 83 | 99:1 | 95 |
| 2 | **1b** | 36 | 21 | 99:1 | 93 |
| 3 | **1c** | 24 | 65 | >99:1 | 96 |
| 4 | **1d** | 24 | trace | | |
| 5 | **1e** | 24 | NR | | |
| 6 | **1f** | 36 | 45 | 94:6 | 70 |

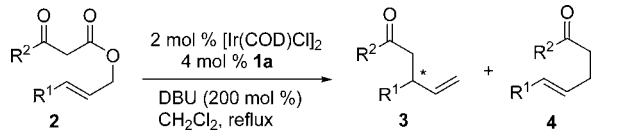
[a] Reactions were conducted under the conditions of entry 6, Table 1. [b] Isolated yields. [c] Determined by $^1H$ NMR after a short silica gel column. [d] Determined by chiral HPLC analysis (Chiralcel OD-H).

**1b** and **1c**, varying the substituents on the amine moiety, afforded the products in low yields, although slightly higher selectivities were given with ligand **1c** (entries 1−3, Table

2). Ligands **1d**,**e** bearing aromatic substituents on the 3,3′-positions of the binaphthyl scaffold were not effective for the reaction (entries 4 and 5, Table 2). The catalyst derived from **1f**, the diastereoisomer of **1a**, could catalyze the reaction in a lower yield and selectivity (entry 6, Table 2).

In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, and 2 equiv of DBU in refluxing $CH_2Cl_2$, decarboxylative allylic alkylation of various substituted allyl $\beta$-ketocarboxylates was carried out to test the generality of the reaction. As summarized in Table 3, allyl $\beta$-ketocarboxylates derived from

**Table 3.** Ir-Catalyzed Decarboxylative Allylic Alkylation[a]



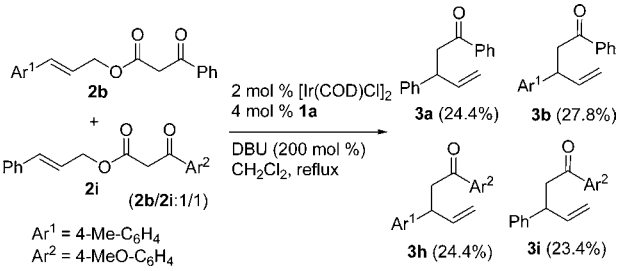

| entry | 2, $R^1$, $R^2$ | time (h) | yield[b] (%) | 3/4[c] | 3, ee[d] (%) |
|---|---|---|---|---|---|
| 1 | **2a**, Ph, Ph | 16 | 83 | 99:1 | **3a**, 95 |
| 2 | **2b**, 4-Me−$C_6H_4$, Ph | 4 | 75 | >99:1 | **3b**, 95 |
| 3 | **2c**, 4-MeO−$C_6H_4$, Ph | 12 | 70 | >99:1 | **3c**, 95 |
| 4 | **2d**, 3-MeO−$C_6H_4$, Ph | 20 | 59 | 99:1 | **3d**, 93 |
| 5 | **2e**, 4-$CF_3$-$C_6H_4$, Ph | 17 | 71 | >99:1 | **3e**, 91 |
| 6 | **2f**, 4-F−$C_6H_4$, Ph | 15 | 67 | >99:1 | **3f**, 94 |
| 7 | **2g**, 2-furyl, Ph | 3 | 73 | 98:2 | **3g**, 94 |
| 8 | **2h**, 4-Me−$C_6H_4$, 4-MeO−$C_6H_4$ | 3 | 58 | >99:1 | **3h**, 96 |
| 9 | **2i**, Ph, 4-MeO−$C_6H_4$ | 4 | 67 | 99:1 | **3i**, 95 |
| 10 | **2j**, Ph, 4-Me−$C_6H_4$ | 12 | 62 | 98:2 | **3j**, 93 |
| 11 | **2k**, Ph, 2-naphthyl | 16 | 71 | 98:2 | **3k**, 93 |
| 12 | **2l**, Me, Ph | 21 | 61 | 94:6 | **3l**, 90 |
| 13 | **2m**, $n$-$C_5H_{11}$, Ph | 22 | 52 | 80:20 | **3m**, 89 |

[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, 0.2 mmol of **2a** in 2 mL of $CH_2Cl_2$. [b] Isolated yields. [c] Determined by $^1H$ NMR after a short silica gel column. [d] Determined by chiral HPLC analysis.

$\gamma$-aryl allyl alcohols formed products with benzylic stereocenters with high regio- and enantioselectivity (entries 1−6). Substrates bearing either electron-donating groups (**2b**−**d**) or electron-withdrawing groups (**2e**,**f**) were well-tolerated. The reaction of 2-furyl-substituted allylic $\beta$-ketocarboxylate **2g** occurred with the same level of regio- and enantioselectivity (entry 7). Several $\beta$-aryl ketocarboxylate substrates **2h**−**k**, which would generate different aryl methyl ketone enolates, all underwent the decarboxylative reaction to deliver their corresponding alkylation products with high regio- and enantioselectivity (entries 8−11). Under the same conditions, two substrates **2l** and **2m** derived from $\gamma$-alkyl allyl alcohols gave the decarboxylative alkylation products in relatively low yields with slightly low regio- and enantioselectivities, as well (entries 12 and 13). The absolute configuration of alkylation products **3a**, **3c**, **3e**, and **3g** was assigned to be (*S*) by comparison of the optical rotation of the literature data.[4a] The stereochemistry of the decarboxylative allylic alkylation reactions parallels that of the intermolecular reactions reported by Hartwig et al.[4a]

To gain insights into the reaction mechanism, a crossover experiment has been carried out by subjecting an equimolar amount of **2b** and **2i** to the standard reaction conditions (Scheme 1). As determined by GC, all four possible branched

**Scheme 1.** Crossover Experiment of **2b** and **2i**




products **3a**, **3b**, **3i**, and **3h** were generated almost equally, which excludes the possibility that the alkylation products are formed through intramolecular rearrangement or the cage ion pairs.[6c]

In summary, we have found that the $[Ir(COD)Cl]_2$/phosphoramidite ligand is an efficient catalytic system for the highly regio- and enantioselective decarboxylative alkylation of $\gamma$-substituted allyl $\beta$-ketocarboxylates, which employs ketone enolates as the nucleophiles and affords the branched products from unsymmetrical allylic substrates. The ready availability of the starting material, mild reaction conditions, and high enantioselectivity of the products make the current method particularly interesting in organic synthesis. Further study on the reaction mechanism and on extending the reaction scope is currently underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and analysis data for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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