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Asymmetric Allylic Alkylation of Ketone Enolates: An Asymmetric Claisen Surrogate

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ABSTRACT

The combination of catalytic palladium(0) and Trost ligand provides an effective catalyst for the rearrangement of allyl *β*-ketoesters. The mechanism of the transformation involves formation of *π*-allyl palladium intermediates which undergo enantioselective attack by ketone enolates. Decarboxylation of *β*-ketocarboxylates allows regiospecific generation of enolates under extremely mild conditions.

Asymmetric catalysis of Claisen-type rearrangements is currently receiving much attention. Despite the recognized synthetic utility of Claisen rearrangements, a general asymmetric catalytic transformation remains elusive.[1,2] The majority of attempts at catalysis have focused on Lewis acid activation, despite the fact that both anionic[3] and cationic[4] acceleration of Claisen rearrangements are possible. Asymmetric catalysis of Claisen rearrangements utilizing Lewis acid activators was initially unsuccessful because the product aldehydes are stronger Lewis bases than the allyl vinyl ether reactants.[5] This problem has been addressed by increasing the Lewis basicity of the allyl vinyl ethers by attachment of pendant groups capable of chelating Lewis acids.[6] We reasoned that a nucleophilic approach toward catalysis may prove complementary to these existing methods. Recently, we proved this concept by showing that pentamethylcyclopentadienylruthenium(II) complexes efficiently catalyze the decarboxylative rearrangement of allyl-*β*-keto carboxylates.[7,8] These substrates are easily synthesized and readily activated by nucleophilic catalysts, producing metal allyl complexes and enolates which react to form γ,δ-unsaturated carbonyl compounds.

Herein we report that high levels of asymmetric induction can be obtained in the palladium-catalyzed decarboxylative rearrangement of allyl-*β*-keto carboxylates.

Saegusa and Tsuji were the first to utilize palladium for the rearrangement of allyl-*β*-ketoesters.[9] The rearrangement is thought to occur through the intermediacy of palladium

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(1) (a) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem*. **2002**, 1461−71. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev*. **1999**, *28*, 43−50.

(2) (a) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2001**, *123*, 2911−2912. (b) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc*. **2003**, *125*, 12412−12413.

(3) (a) Denmark, S. E.; Marlin, J. E. *J. Org. Chem*. **1987**, *52*, 5742−3. (b) Denmark, S. E.; Harmata, M. A. *J. Org. Chem*. **1983**, *48*, 3369−3370. (c) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc*. **1985**, *107*, 5572−5573.

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(5) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc*. **1995**, *117*, 1165−1166.

(6) (a) Abraham, L.; Czerwonka, R.; Hiersmann, M. *Angew. Chem., Int. Ed*. **2001**, *40*, 4700−4703. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc*. **2000**, *122*, 3785−3786.

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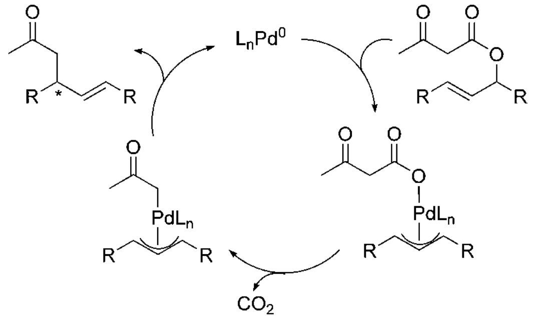
(9) (a) Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc*. **1980**, *102*, 6381−6384. (b) Tsuji, J. *Pure Appl. Chem*. **1982**, *54*, 197−206. (c) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M. Shimizu, I. *J. Org. Chem*. **1987**, *52*, 2988−2995.

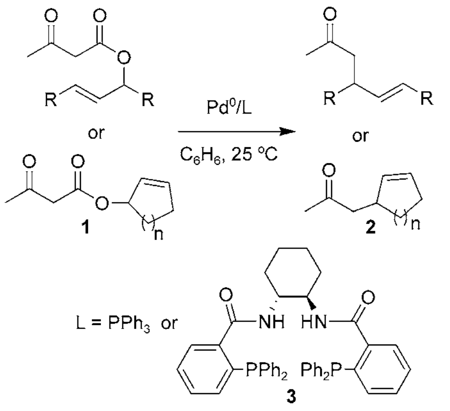
10.1021/ol048149t CCC: $27.50

Scheme 1



π-allyl complexes which undergo nucleophilic attack by enolates (Scheme 1).[10]

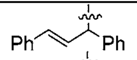
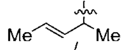
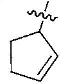
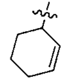
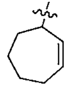
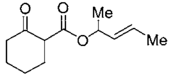
Scheme 2



Initially, we studied the rearrangement of disubstituted allyl carboxylates because rearrangement of these substrates has not been previously reported (Scheme 2). The rearrangement occurred smoothly, albeit slowly, at room temperature utilizing 10 mol % $Pd(PPh_3)_4$ in C_6H_6 (Table 1).

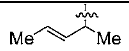
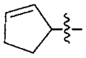
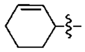
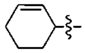
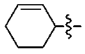
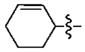
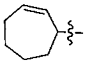
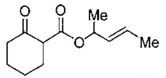
Next, we investigated the asymmetric variant using $Pd_2(dba)_3$ and Trost's ligand (**3**).[11] Gratifyingly, high levels of asymmetric induction were observed for cyclic and methyl-substituted allyl compounds (Table 2). For instance, treatment of **1b** with 5 mol % $Pd_2(dba)_3$ and 10 mol % ligand in C_6H_6 for 15 h provided a 93:7 ratio of enantiomers. Raising the loading of ligand to 15 mol % resulted in a significant decrease in the enantioenrichment of the product. This behavior has been noted by others and has been attributed to the stoichiometry of the catalyst−ligand complex.[12] The reaction time can be significantly reduced by running the reactions in refluxing C_6H_6, with little effect on the enantioselectivity of enolate addition. Under optimized conditions, **1c** undergoes rearrangement in the presence of 0.2 mol % Pd_2dba_3 and 0.4 mol % L in refluxing benzene to give 71% isolated yield of **2c** as a 94:6 ratio of enantiomers (>175 TOs).

Table 1. $Pd(PPh_3)_4$-Catalyzed Rearrangements of $CH_3COCH_2CO_2R$[a]

substrate	R	time (h)	yield %
1a		1	94
1b		15	85
1c		15	69
1d		24	87
1e		45	83
1f		48	69

[a] Reaction times and isolated yields for 0.3 M substrate and 10 mol % $Pd(PPh_3)_4$ in C_6H_6 at 25 °C.

Table 2. Asymmetric Palladium-Catalyzed Rearrangements of $R_1COCH_2CO_2R_2$

R^1	R^2	time h	er 25 °C (80 °C)	yield %
Me		15 (0.5)	93:7 (92:8)	82
Me		15 (18)	93:7 (94:6)[a]	85 (71)
Me		24 (0.5)	97:3 (95:5)	75
$PhCH_2$		27	95:5	71
i-Pr		18[b]	90:10	94
Ph		18	96:4	69
Me		45 (0.5)	99:1 (99:1)	81
		187 (1)	77:23[c] (73:27)	81

[a] 0.2 mol % Pd_2dba_3 [b] Reaction temperature = 50 °C. [c] er is that of the major diastereomer; dr = 1.5.

A variety of terminal enolates are regiospecifically generated by decarboxylation and allylated with high enantioselectivities (Table 2). Cyclic enolates are also viable partners; however, the enolate of cyclohexanone is not very selective, and product is formed in modest er and low dr.

The palladium-catalyzed decarboxylative rearrangement is equivalent to the addition of nonstabilized ketone enolates to palladium allyl complexes.[13] Since the products formed by our method can be accessed through asymmetric allylic alkylation (AAA) utilizing sodium ethylacetoacetate as a

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(10) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(11) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343.

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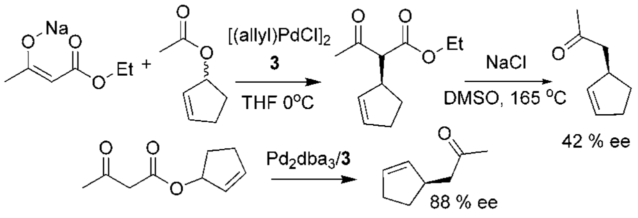
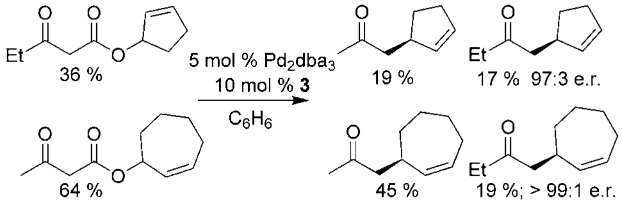
nucleophile followed by hydrolysis and decarboxylation, it is worth comparing the two methods. Using **1c** as a standard, our yield and selectivity (85%, 93:7) can be compared to that reported for the addition of sodium dimethylmalonate to 2-cyclopentenyl acetate with the same ligand (77%, 69:31).[14] To assign the absolute stereochemistry of a decarboxylative allylation product we compared it with the identical product derived from AAA. Thus, cyclopentenyl acetate was treated with sodium ethylacetoacetate in THF at 0 °C (Scheme 3).[14] The resulting substitution product was decarboxylated to give *R*-**2c** as the major enantiomer (71:29 *R*/*S*). The major enantiomer resulting from the decarboxylative rearrangement of **1c** is also the *R* enantiomer. This experiment suggests that nonstabilized ketone enolates attack the allyl ligand from the face opposite of Pd, consistent with the observation of complete scrambling in a crossover experiment (Scheme 4).

Scheme 3

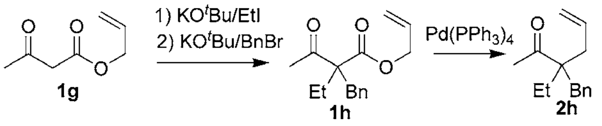


Scheme 4



To test whether decarboxylation occurs prior to the C−C bond-forming step, we prepared an allyl *β*-ketoester having a quaternary α-carbon (Scheme 5). Such a compound can undergo the allylation reaction only if decarboxylation occurs prior to the C−C bond-forming step. Compound **1h** undergoes Pd-catalyzed decarboxylative allylation at a similar rate to other substrates. Thus, decarboxylation likely precedes nucleophilic attack indicating that ketone enolates are true intermediates. Additionally, because the product **2h** cannot be made using the traditional Tsuji-Trost reaction, these transformations highlight the potential power of decarboxylative allylation.

Scheme 5



In summary, nucleophilic Pd^0 complexes are effective catalysts for asymmetric decarboxylative allylic alkylation. Mechanistically, the reaction involves the asymmetric allylation of ketone enolates that are regiospecifically generated in situ under base-free and tin-free conditions. Compared to known allylations of enolates, the method described here is superior in atom economy,[15] step economy,[16] and mildness of reaction conditions. Future work will extend asymmetric decarboxylative allylation to prochiral enolates.

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

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(13) a) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z *Org. Lett.* **2000**, *3*, 149−151. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759−6760. (c) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3494−3497.

(14) (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089−4090. (b) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70−79.

(15) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705.

(16) Wender, P. A.; Miller, B. L. *Org. Synth.: Theory Appl.* **1993**, 27−66.