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Catalytic Enantioselective Decarboxylative Protonation

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Enantioselective protonation represents a direct method for generating tertiary carbon stereocenters from an achiral enolate or an enol equivalent. Several distinct approaches toward effecting this process have been reported, including the use of achiral enolates with chiral Brønsted acids, chiral metal enolates with an achiral proton source, and the combination of chiral enolates and chiral Brønsted acids.[1] Of the existing methods, most are limited in scope, few are catalytic, and together they have not provided a general solution to this deceptively simple goal.[1d] Herein, we report a highly enantioselective, general catalytic system for the facile synthesis of tertiary stereocenters by protonation adjacent to ketones.

Recently, we disclosed a series of catalytic enantioselective allylation reactions that deliver cyclic ketones bearing all-carbon quaternary stereocenters at the α-position with high efficiency and enantioselectivity.[2,3] Crucial to the success of these transformations was the use of catalysts derived from Pd(0) and a chiral phosphinooxazoline (PHOX) supporting ligand (e.g., **1**).[4] Included in this effort was our exploration of racemic allyl β-ketoesters as substrates for a novel stereoablative enantioconvergent decarboxylative allylation reaction (e.g., (±)-**2** → **4**, Scheme 1).[3] We believe that in the course of this reaction a chiral Pd-enolate (**3**) likely is generated in solution and that the high degree of organization about the palladium center is responsible for the levels of enolate facial selectivity observed in the alkylation. Interestingly, if this were the case, the catalytic generation and utilization of such chiral enolate complexes by this method would have the potential to be more broadly applicable than we previously recognized. Thus, in an effort to exploit this valuable chiral synthon, we chose to intercept this intermediate with an alternative electrophile, namely, a proton.[5,6]

In our first attempt to achieve an enantioselective protonation, racemic β-ketoester (±)-**2** was exposed to $Pd(OAc)_2$ in the presence of (*S*)-*t*-Bu-PHOX (**1**) with triethylamine and HCO_2H, resulting in smooth conversion to 2-methyl-1-tetralone with low, but measurable, enantiomeric excess (entry 1, Table 1).[5] Although necessary in a nonenantioselective version of the protonation reported by Tsuji,[5] removal of the amine base in our asymmetric system led to improved, though still quite modest, enantiomeric excess (entry 2). To sequester the small amount of water present in commercially available formic acid, we added 3 Å molecular sieves (MS) to the reaction mixture. Gratifyingly, we found that this additive provided **5** in dramatically increased enantiopurity (entry 3). A screen of alternative Pd sources and solvents revealed the superiority of $Pd(OAc)_2$ to other Pd precursors and *p*-dioxane as the preferred solvent (entries 3−6).[7] Investigation of other potential drying agents indicated their inferiority relative to MS, and, specifically, 4 Å MS provided the highest enantiomeric excess of the observed products (entries 6−8).[7] At this point, we also examined the behavior of other chiral ligands in this reaction. As in our earlier studies,[2] we found chelating P−N ligands to be the most effective, while bisphosphine-type ligands provided only trace asymmetric induction (entries 9−14). Finally, we found that when the solvent was freshly distilled and the 4 Å MS were rigorously flame-dried immediately prior to use, the enantiomeric purity was further enhanced, providing **5** in 92% ee (entry 15).

Scheme 1

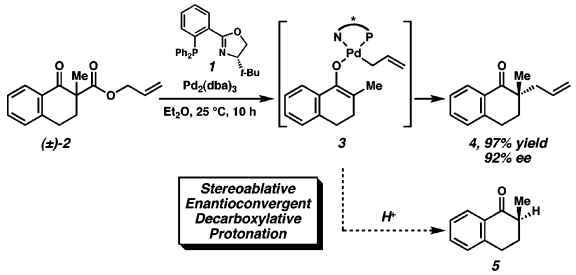
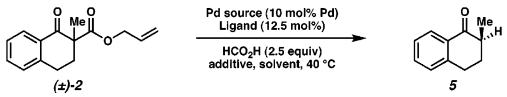


Table 1. Optimization of Reaction Conditions[a]



entry	Pd source	ligand	additive[b]	solvent	ee[c] (%)
1	$Pd(OAc)_2$	**1**	Et_3N (1 equiv)	THF	7
2	$Pd(OAc)_2$	**1**	none	THF	24
3	$Pd(OAc)_2$	**1**	3 Å MS	THF	72
4	$[Pd(allyl)Cl]_2$	**1**	3 Å MS	THF	41
5	$Pd_2(dba)_3$	**1**	3 Å MS	THF	49
6	$Pd(OAc)_2$	**1**	3 Å MS	*p*-dioxane	79
7	$Pd(OAc)_2$	**1**	4 Å MS	*p*-dioxane	88
8	$Pd(OAc)_2$	**1**	5 Å MS	*p*-dioxane	85
9	$Pd(OAc)_2$	(*R*)-BINAP	4 Å MS	*p*-dioxane	−1
10	$Pd(OAc)_2$	(*R*,*R*)-DIOP	4 Å MS	*p*-dioxane	3
11	$Pd(OAc)_2$	(*R*,*R*)-Trost ligand	4 Å MS	*p*-dioxane	3[d]
12	$Pd(OAc)_2$	(*S*)-QUINAP	4 Å MS	*p*-dioxane	−20
13	$Pd(OAc)_2$	(*R*)-Ph-PHOX	4 Å MS	*p*-dioxane	−65
14	$Pd(OAc)_2$	(*S*)-*i*-Pr-PHOX	4 Å MS	*p*-dioxane	87
15[e]	$Pd(OAc)_2$	**1**	4 Å MS	*p*-dioxane	92

[a] Reactions performed with 0.1 mmol of (±)-**2** at 0.033 M in solvent and run to complete consumption of (±)-**2**. [b] Where indicated, 90 mg of MS was used. [c] Determined by chiral HPLC. [d] Measured after 72 h at approximately 60% conversion. [e] *p*-Dioxane was freshly distilled over Na metal and the 4 Å MS were flame dried under vacuum prior to use. Reaction performed with 0.2 mmol of (±)-**2** and 180 mg of 4 Å MS.

Attempts to optimize the amount of HCO_2H and 4 Å MS in the reaction indicated that the balance of these two components was intimately related to both enantio- and chemoselectivity (i.e., the ratio of protonated to allylated products **5**/**4**).[7] In general, an excess of HCO_2H led to decreased enantioselectivity, while smaller quantities afforded greater amounts of allylated product **4**. Alternatively, small amounts of 4 Å MS produced **5** in decreased ee, while large quantities led to increased allylation. For this particular substrate, the optimal amount of HCO_2H was found to be 6.0 equiv with a 4 Å MS quantity of 1.80 g/mmol substrate. Under these conditions, (*S*)-(−)-2-methyl-1-tetralone (**5**) was produced in 88% yield and 94% ee with no observable allylation (Table 2, entry 1).[8,9]

Encouraged by these studies, we sought to explore the generality and scope of this enantioselective reaction (Table 2). A variety of

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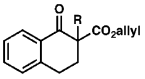
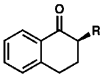
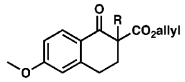
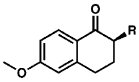
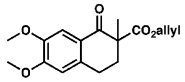
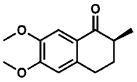
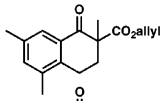
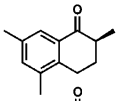
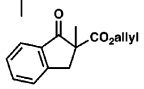
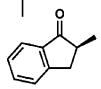
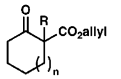
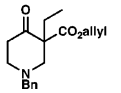
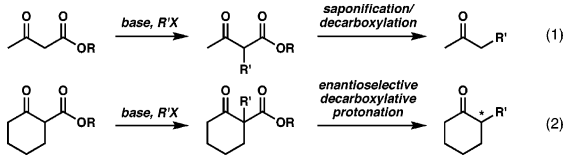
Table 2. Enantioconvergent Decarboxylative Protonations

entry	substrate	product		time (h)	yield[a](%)	ee[b](%)
1			R = Me	10	88	94 (*S*)
2			R = allyl	4	88	85 (*R*)
3			R = F	5	79	88 (*S*)
4			R = Me	5	91	95
5			R = allyl	6	81	88
6			R = Bn	5	95	78
7				8.5	62	94
8				8	75	92
9[c]				22	83	81 (*S*)
10			n = 0, R = Bn	4	63	60
11			n = 1, R = Me	4.5	99[d]	85 (*R*)
12[e]			n = 1, R = Bn	4.5	91	92 (*S*)
13			n = 2, R = Bn	5	69	74
14				3	81	84

[a] Isolated yield from the reaction of 0.3 mmol of substrate at 0.033 M in *p*-dioxane with 10 mol % $Pd(OAc)_2$, 12.5 mol % (*S*)-*t*-Bu-PHOX, 5−8 equiv HCO_2H, and 405−810 mg of 4 Å MS at 40 °C (ref 7). [b] Determined by chiral HPLC or GC; where noted, the absolute configuration was determined by comparing the sign of optical rotation to literature values (ref 7). [c] Reaction performed with 5 mol % $Pd(OAc)_2$ and 6.25 mol % (*S*)-*t*-Bu-PHOX. [d] GC yield using tridecane as internal standard. [e] Reaction performed at 35 °C.

substitutions is tolerated at the ketone α-position (entries 1−3) and various positions about the aromatic ring (entries 4−8) of 1-tetralone derivatives. Enantioenriched (*S*)-(+)-2-methyl-1-indanone can also be produced from the corresponding *β*-ketoester (entry 9). Additionally, monocyclic compounds (entries 10−13) and a heterocycle (entry 14) were easily accessed under similar reaction conditions. The absolute configuration of a number of products was established by a comparison of the observed sign of optical rotation to literature values (entries 1−3, 9, 11, and 12).[7] Interestingly, fused aromatic substrates (i.e., tetralones and indanones) lead to products in the opposite enantiomeric series compared to that of the cyclohexanone cases (cf. entries 1−3 and 9 to entries 11 and 12). These results are in contrast to the consistent enantiofacial selectivity observed across multiple substrate types in our asymmetric allylation chemistry and suggest stark differences in their corresponding mechanisms.[2,3]

In conclusion, a novel system for the enantioconvergent decarboxylative protonation of racemic *β*-ketoesters has been developed. The reaction tolerates a variety of substitution and functionality and delivers products of high enantiopurity in excellent yield. The enantioinduction in the observed protonated products is consistent with the intermediacy of an enolate that is intimately associated to the chiral Pd complex. This, in turn, substantiates our initial hypothesis concerning the nature of the reactive intermediate **3** and opens the door to further applications. The process capitalizes on the availability and unique reactivity of racemic α-substituted allyl-*β*-ketoesters, which are employed directly in the catalytic enantioselective process and deliver valuable tertiary-substituted products in highly enantioenriched form. In general, the overall process (substrate synthesis and use) represents a catalytic enantioselective variant of classic alkylation/decarboxylation sequences (e.g., acetoacetic ester synthesis, cf. eqs 1 and 2). Furthermore, the asymmetric protonation described here serves to complement our recently developed asymmetric alkylation methodology that delivers quaternary stereocenters from the same starting materials via catalytic enantioselective allylation. Additional explorations of the scope, mechanism, and applications of these technologies are currently underway.[10]



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

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(1) For reviews of enantioselective protonation, see: (a) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653−3691. (b) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 1295−1306. (c) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; Supplement 2, pp 125−132. (d) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566−2587.

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(5) A nonenantioselective decarboxylative protonation has been reported by Tsuji, see: (a) Tsuji, J.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1985**, *50*, 3416−3417. (b) Mandai, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 5395−5397.

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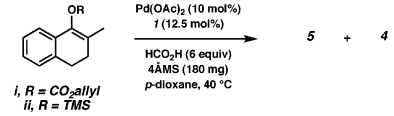
(7) See the Supporting Information for details.

(8) Despite extensive experimentation to verify the origin of the proton observed in the products (i.e., **5**), we have maximally observed 35% D-incorporation when using HCO_2D and rigorously dried 4 Å MS. By contrast, under otherwise identical conditions, <1% D-incorporation was observed when DCO_2H was employed.[7] The detailed mechanism of proton incorporation (e.g., proton transfer, reductive elimination, or otherwise) remains unclear and is under investigation.

(9) We were interested in whether the other enolate precursors we have employed for enantioselective allylation chemistry would be competent substrates for the protonation reaction. To investigate this possibility, allyl enol carbonate **i** was subjected to our optimized reaction conditions for the formation of **5**. Contrasting the result when (±)-**2** was used (Table 2, entry 1), in this case, **5** was produced in 74% ee with a 66/44 ratio of **5**/**4** on a 0.1 mmol scale (100% conversion). When enol silane **ii** was used, low conversion (<5%) was observed, however, the ee of isolated **5** was 84%. While these results highlight the advantage of *β*-ketoester precursors to the reactive enolate intermediate, it is uncertain why the reactivity and selectivity of these substrates is so different. The mechanism of this process is currently under investigation.



(10) We recently completed the first asymmetric synthesis of (+)-dichroanone using our catalytic enantioselective Tsuji allylation, see: McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738−7739.

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