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Asymmetric Retro-Claisen Reaction by Synergistic Chiral Primary Amine/Palladium Catalysis

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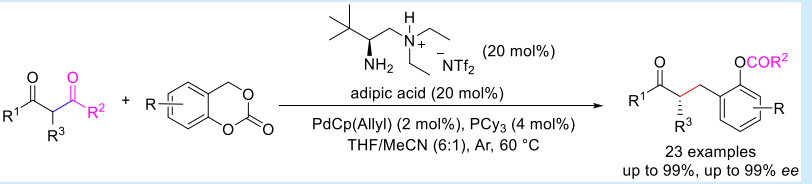
Supporting Information

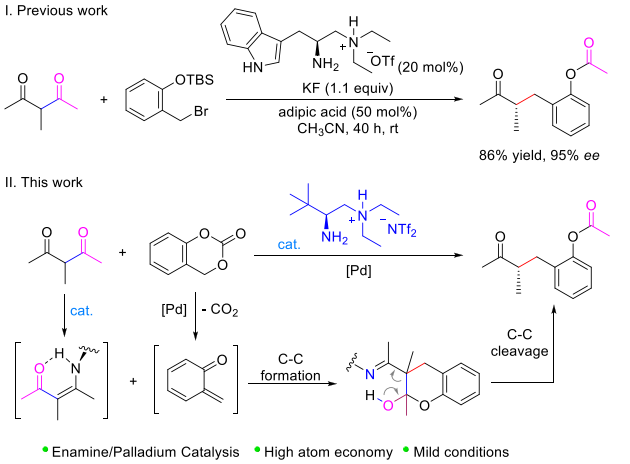


ABSTRACT: We described herein a chiral primary amine/palladium catalyzed asymmetric retro-Claisen reaction of β-diketones with salicylic carbonates. A series of chiral α-alkylated ketones and macrolides were obtained with good yields and excellent enantioselectivities upon a sequence of decarboxylative benzylation, retro-Claisen cleavage, and enamine protonation. This strategy features broad substrate scope, mild conditions, as well as high atom economy with salicylic carbonates as the *o*-quinone methide precursors.

As fundamental C−C bond formation and cleavage strategies, Claisen reaction and its retro process have been widely applied in organic synthesis for the construction of new scaffolds such as long-chain keto-acids, macrocycles, and complex natural products and fine chemicals.[1] The resulting β-dicarbonyl moiety also serves as a versatile precursor in late-stage synthesis.[2] In recent years, great progress has been made in the catalytic retro-Claisen reaction by the catalysis with Lewis acid,[3] Brønsted acid,[4] or Brønsted base.[5] However, catalytic asymmetric versions remained largely under-developed. Duthaler first reported an asymmetric retro-Claisen reaction of prochiral bicyclic β-diketones with moderate stereoselectivity using a stoichiometric amount of chiral bases as nucleophiles.[6] Later on, Grogan disclosed the first enzyme-catalyzed asymmetric retro-Claisen reaction for the desymmetrization of cyclic β-diketones.[7] In this strategy, 6-oxocamphor hydrolase plays a crucial role to provide a chiral environment, activate nucleophilic water molecule, and stabilize the enolate oxyanion ion intermediate.[8] Afterward, a phase-transfer catalyzed retro-Claisen reaction of a specific racemic β-diketone was described by Tokunaga, and only a single substrate was examined in this study.[9] These three examples all involved enol-protonation as the key stereogenic step, and the scopes were rather limited.

Recently, our group developed an enamine strategy for asymmetric retro-Claisen reaction of β-diketones by merging chiral primary amine catalysis and Lewis base activation (Scheme 1, I).[10] This reaction proceeded via a tandem stereoselective C−C coupling/C−C cleavage/enamine protonation to provide chiral α-tertiary ketones and macrolides with excellent yields and enantioselectivities. However, the reaction relied on a heterogeneous acid−base buffer system involving a stoichiometric amount of KF and large loading of acid additives, which is critical for the *in situ* generation of *ortho*-quinone methide via fluoride anion mediated desilylation, thus diminishing its applicability (Scheme 1, I). In seeking a homogeneous reaction setting, we now reported the use of the salicylic carbonate (benzo-1,3-dioxan-2-one)[11] for enamine-based retro-Claisen reaction. Though substituted benoxazi-

Scheme 1. Catalytic Asymmetric Retro-Claisen Reaction



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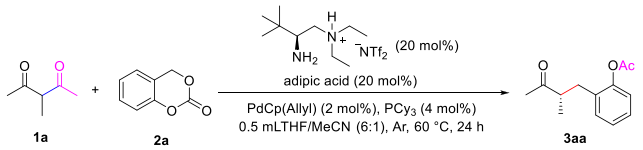
nones have been widely applied in transition metal-promoted decarboxylative transformations,[12,13] the unsubstituted one, i.e., salicylic carbonates, have surprisingly not been explored in similar reactions. We found that a palladium catalyst could facilitate the decarboxylative generation of *ortho*-quinone methide from this salicylic carbonate (Scheme 1, II). Hence, the synergistic catalysis with our chiral primary amine and palladium complex allowed for effective decarboxylative benzylation/retro-Claisen cascade in an atom-economic and highly enantioselective manner under neutral and homogeneous conditions.

We initiated our investigation with the model reaction shown in Table 1. 3-Methyl-2,4-pentanedione **1a** was treated with the salicylic carbonate **2a** in the presence of chiral primary amine catalyst, Pd catalyst, and acid additive. To our delight, the desired C−C bond cleavage product **3aa** was obtained in 73% yield and 96% ee under the optimized conditions (Table 1, entry 1). No desired product was observed in the absence of aminocatalyst, suggesting the enamine catalysis process (Table 1, entry 2). The use of acidic additive improved the yield greatly, without affecting the enantioselectivity (Table 1, entry 3). Optimization of the palladium complex led to the identification of PdCp(allyl) (2 mol %) with PCy_3 (4 mol %) as the optimal catalyst. Control experiments revealed that the reaction in the absence of palladium complex was rather sluggish (Table 1, entries 4−6). Decreasing the ligand/palladium ratio from 2:1 to 1:1 also led to a reduction in yield (Table 1, entry 7), an indication of the critical role of palladium complex in promoting the reaction likely by facilitating the decarboxylation step. The reaction conditions were further optimized (Table 1, entries 8−12). A mixture of THF/MeCN (6:1) as solvent was found to give the best results in terms of both yield and enantioselectivity. Slightly heating at 60 °C was required for complete conversion (entry 10 vs entry 1). When free salicylic alcohol or salicylic acid was used, no reaction was observed (not shown). Finally, an optimal 91% yield and 95% ee could be obtained when prolonging the reaction time to 48 h under the optimized conditions (entry 11).

Table 1. Screening and Optimization

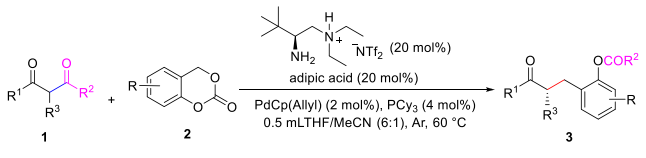


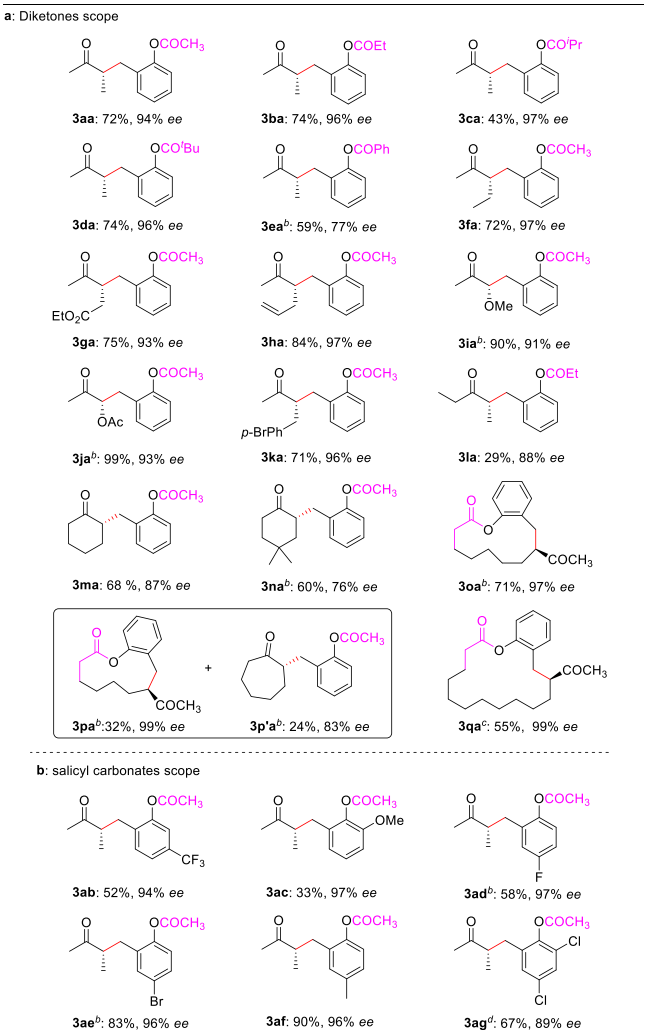
entry	variation from standard conditions[a]	yield (%)[b]	ee (%)[c]
1	none	73	96
2	no aminocatalyst	n.p.	
3	no adipic acid	25	97
4	no PdCp(allyl)	34	97
5	no PCy_3	21	97
6	no PdCp(allyl), no PCy_3	32	97
7	2.5 mol % PdCp(allyl), 2.5 mol % PCy_3	53	95
8	0.5 mL THF	35	97
9	0.5 mL MeCN	92	83
10	40 °C	trace	n.d.
11	**48 h**	**91**	**95**

[a]Standard reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), chiral amine (20 mol %), adipic acid (20 mol %), PdCp(allyl) (2 mol %), PCy_3 (4 mol %), 0.5 mL THF/MeCN(6/1), Ar, 60 °C, 24 h. [b]NMR yield measured by using 1,3,5-tirmethoxybenzene as the internal standard. [c]Determined by HPLC analysis.

Having optimized the reaction conditions, we first examined the functional-group tolerance of the reaction with the *β*-diketones. Most *β*-diketones reacted well to give the desired retro-Claisen cleavage products in good yields and excellent enantioselectivities (Table 2, **3aa**−**3da**), in the case of phenyl ketone, the enantioselectivity was moderate (Table 2, **3ea**). It is noted that the C−C bond cleavage occurred exclusively on the more bulky keto side in these reactions, suggesting that the chiral primary amine catalyst was able to differentiate two different keto groups to form an enamine intermediate with the smaller keto moiety. A variety of symmetrical diketones with different *α*-alkyl or *α*-heteroatom substituents could also be

Table 2. Substrate Scope[a]





[a]All reactions were performed with **1** (0.1 mmol), **2** (0.2 mmol), chiral amine (20 mol %), adipic acid (20 mol %), PdCp(allyl) (2 mol %), and PCy_3 (4 mol %) in 0.5 mL of THF/MeCN(6/1) at 60 °C under Ar. Yield of isolated product. Determined by HPLC analysis. [b]72 h. [c]95 h. [d]15 h.

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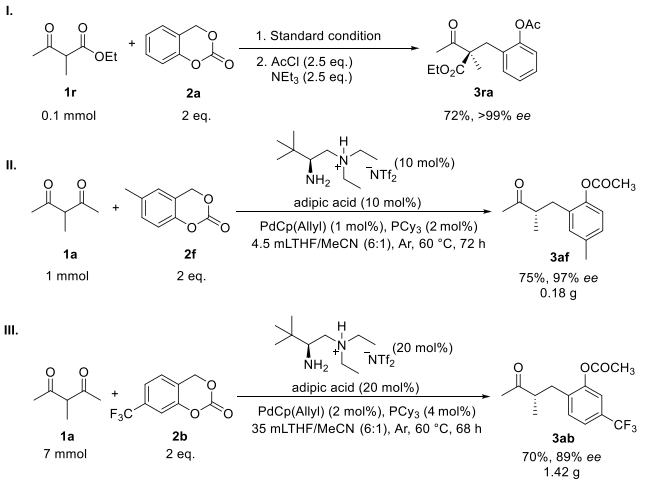
tolerated to give the expected products in 71−99% yields with 91−97% ee (Table 2, **3fa**−**3ka**). A symmetrical ethyl substituted diketone also worked, albeit with low reactivity and moderate enantioselectivity (Table 2, **3la**).

Cyclic β-diketones were next examined. 2-Acetylcyclopentanone, dominantly in its enol form, was not a workable substrate in this reaction (not shown). In contrast, 2-acetylcyclohexanone worked well to give 68% yield and 87% ee (Table 2, **3ma**). 4-Substituted 2-acetylcyclohexanone was also applicable to deliver the desired products in 60% yield and 76% ee (Table 2, **3na**). In the case of 2-acetylcycloheptanone, the reaction furnished two C−C bond cleavage adducts, corresponding to the major ring-enlarged macrolide in 32% yield with 99% ee and the minor deactylation product in low activity and poor enantioselectivity, respectively (Table 2, **3pa** and **3p′a**). When 2-acetylcyclooctanone was employed in the reaction, a sole macrolide product was obtained in 71% yield and 97% ee (Table 2, **3oa**). A large 2-acetylcyclododecanone was also examined and could be converted into the desired macrolide product in moderate yield and excellent enantioselectivity (Table 2, **3qa**). It should be noted it remains a challenging subject to prepare large ring chiral macrolides in asymmetric synthesis.

We then explored the scope of salicylic carbonates. Salicylic carbonates bearing either electron-donating or electron-withdrawing groups on the arene moiety participated in the reaction smoothly to furnish the desired products in 33−90% yields with 94−97% ee (Table 2, **3ab**−**3af**). The highly active dichloro-substituted salicylic carbonate could also be incorporated to the expected product in 67% yield and 89% ee in less than 15 h (Table 2, **3ag**). When the β-ketoester substrate **1r** was employed to react with the carbonate **2a** under standard conditions, no desired retro-Claisen cleavage product was detected. Not unexpectedly, the reaction provided a single α-benzylation adduct **3ra** in 72% yield and >99% ee after acyl protection of the free phenol moiety (Scheme 2, I).[14]

To evaluate the practicality of the current reaction, we performed a 1 mmol scale with β-diketone **1a** and **2f** in the presence of only 10 mol % of primary amine catalyst and 1 mol % of Pd catalyst. The desired product was obtained in 75% yield and 97% ee with a prolonged reaction time (Scheme 2, II). The low catalyst loading only slightly reduced the yield, without affecting the enantioselectivity. We also performed a gram-scale experiment on the 7 mmol scale with β-diketone **1a** and the cyclic carbonate **2b** under standard conditions. The desired product was obtained in comparable 70% yield and 89% ee (Scheme 2, III).

Scheme 2. (I) Reaction of the β-Ketoester with Salicylic Carbonate under Standard Conditions and (II and III) Scale-Up Experiments



In summary, we have developed a highly atom-economic symmetric retro-Claisen reaction of β-diketones with salicylic carbonates by chiral primary amine/palladium synergistic catalysis. The salicylic carbonate has been proved to be an effective alternative to generate *ortho*-quinone methide precursor via Pd-catalyzed decarboxylation. This synergistic strategy enables the construction of chiral α-tertiary ketones and chiral macrolides with good yields and excellent enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02491.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Jukič, M.; Šterk, D.; Časar, Z. Recent Advances in the Retro-Claisen Reaction and Its Synthetic Applications. *Curr. Org. Synth.* **2012**, *9*, 488−512.

(2) For examples on the use of retro-Claisen reaction in late-stage synthesis, see (a) Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. Enantioselective Cascade Formal Reductive Insertion ofAllylic Alcohols into the C(O)-C Bond of 1,3-Diketones: Ready Access to Synthetically Valuable 3-Alkylpentanol Units. *Org. Lett.* **2014**, *16*, 2802−2805. (b) Shang, Y.-J.; Hu, X.-Q.; He, X.-W.; Tao, J.-J.; Han, G.; Wu, F.-L.; Wang, J. $FeCl_3$-Mediated Synthesis of β-Alkynyl Ketones via Domino Nucleophilic Substitution/Intramolecular-Cyclization/Reverse Claisen Condensation of N-Cyclohexyl Propargylamines and 1,3-Diketones. *J. Org. Chem.* **2015**, *80*, 4760−4765.

(3) For selected examples, see (a) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. Indium-Catalyzed Retro-Claisen Condensation. *Angew. Chem., Int. Ed.* **2007**, *46*, 7793−7795. (b) Kuninobu, Y.; Kawata, A.; Noborio, T.; Yamamoto, S.-I.; Matsuki, T.; Takata, K.; Takai, K. Indium-Catalyzed Synthesis of Keto Esters from Cyclic 1,3-Diketones and Alcohols and Application to the Synthesis of Seratrodast. *Chem. - Asian J.* **2010**, *5*, 941−945. (c) Rao, C. B.; Rao, D. C.; Babu, D. C.; Venkateswarlu, Y. Retro-Claisen Condensation with Fe^{III} as Catalyst

DOI: 10.1021/acs.orglett.9b02491
Org. Lett. XXXX, XXX, XXX−XXX

under Solvent-Free Conditions. *Eur. J. Org. Chem.* **2010**, *2010*, 2855−2859. (d) Biswas, S.; Maiti, S.; Jana, U. An Efficient Iron-Catalyzed Carbon−Carbon Single-Bond Cleavage via Retro-Claisen Condensation: A Mild and Convenient Approach to Synthesize a Variety of Esters or Ketones. *Eur. J. Org. Chem.* **2010**, *2010*, 2861−2866. (e) Wang, S.; Yu, Y.; Chen, X.; Zhu, H.; Du, P.; Liu, G.; Lou, L.; Li, H.; Wang, W. *Tetrahedron Lett.* **2015**, *56*, 3093−3096. (f) Hussein, M. A.; Huynh, V. T.; Hommelsheim, R.; Koenigs, R. M.; Nguyen, T. V. An efficient method for retro-Claisen-type C−C bond cleavage of diketones with tropylium catalyst. *Chem. Commun.* **2018**, *54*, 12970−12973.

(4) For selected examples, see (a) Shen, G.; Zhou, H.; Du, P.; Liu, S.; Zou, K.; Uozumi, Y. Brønsted acid-catalyzed selective C−C bond cleavage of 1,3-diketones: a facile synthesis of 4(3H)-quinazolinones in aqueous ethyl lactate. *RSC Adv.* **2015**, *5*, 85646−85651. (b) Li, Z.; Dong, J.; Chen, X.; Li, Q.; Zhou, Y.; Yin, S.-F. Metal- and Oxidant-Free Synthesis of Quinazolinones from β-Ketoesters with o-Aminobenzamides via Phosphorous acid Catalyzed Cyclocondensation and Selective C-C Bond Cleavage. *J. Org. Chem.* **2015**, *80*, 9392−9400.

(5) For selected examples, see (a) Xie, F.; Yan, F.; Chen, M.; Zhang, M. Base-catalyzed retro-Claisen condensation: a convenient esterification of alcohols via C−C bond cleavage of ketones to afford acylating sources. *RSC Adv.* **2014**, *4*, 29502−29508. (b) Yadav, D. K. T.; Bhanage, B. M. Base-catalyzed synthesis of amides and imines via C−C and C = C bond cleavage. *RSC Adv.* **2015**, *5*, 12387−12391. (c) Cai, G.-X.; Wen, J.; Lai, T.-T.; Xie, D.; Zhou, C.-H. Sequential Michael addition/retro-Claisen condensation of aromatic β-diketones with α,β-unsaturated esters: an approach to obtain 1,5- ketoesters. *Org. Biomol. Chem.* **2016**, *14*, 2390−2394.

(6) Duthaler, R. O.; Maienfisch, P. Asymmetric Induction by Enantiotopically Differentiating *retro-Cluisen* Reaction of Prochiral Bicyclic β-Diketones. *Helv. Chim. Acta* **1984**, *67*, 845−855.

(7) Grogan, G.; Graf, J.; Jones, A.; Parsons, S.; Turner, N. J.; Flitsch, S. L. An Asymmetric Enzyme-Catalyzed Retro-Claisen Reaction for the Desymmetrization of Cyclic β-Diketones. *Angew. Chem., Int. Ed.* **2001**, *40*, 1111−1114.

(8) Leonard, P. M.; Grogan, G. Structure of 6-Oxo Camphor Hydrolase H122A Mutant Bound to Its Natural Product, (2*S*,4*S*)–Campholinic Acid. *J. Biol. Chem.* **2004**, *279*, 31312−31317.

(9) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. Hydrolytic Enantioselective Protonation of Cyclic Dienyl Esters and a β-Diketonewith Chiral Phase-Transfer Catalysts. *Org. Lett.* **2012**, *14*, 6178−6181.

(10) Zhu, Y.; Zhang, L.; Luo, S. Asymmetric Retro-Claisen Reaction by Chiral Primary Amine Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 3978−3981.

(11) Bialas, N. J.; Kuhling, S.; Keul, H.; Hocker, H. On the behaviour of benzo-1,3-dioxolan-2-one and benzo-1,3-dioxan-2-oneversus carbanionic species. *Makromol. Chem.* **1990**, *191*, 1165−1175.

(12) For selected examples, see (a) Guo, C.; Fleige, M.; Janssen-Muller, D.; Daniliuc, C. G.; Glorius, F. Cooperative N-Heterocyclic Carbene/Palladium-Catalyzed Enantioselective Umpolung Annulations. *J. Am. Chem. Soc.* **2016**, *138*, 7840−7843. (b) Wang, Q.; Li, T.-R.; Lu, L.-Q.; Li, M.-M.; Zhang, K.; Xiao, W.-J. Catalytic Asymmetric [4 + 1] Annulation of Sulfur Ylides with Copper-Allenylidene Intermediates. *J. Am. Chem. Soc.* **2016**, *138*, 8360−8363.

(13) For reviews, see (a) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions. *Chem. Rev.* **2011**, *111*, 1846−1913. (b) Le Bras, J.; Muzart, J. Production of Csp^3−Csp^3 Bonds through Palladium-Catalyzed Tsuji−Trost-Type Reactions of (Hetero) Benzylic Substrates. *Eur. J. Org. Chem.* **2016**, *2016*, 2565−2593.

(14) Zhu, Y.; Zhang, W.-Z.; Zhang, L.; Luo, S. Chiral Primary Amine Catalyzed Asymmetric α-Benzylation with In Situ Generated ortho-Quinone Methides. *Chem. - Eur. J.* **2017**, *23*, 1253−1257.

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Org. Lett. XXXX, XXX, XXX−XXX