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Uniting C1-Ammonium Enolates and Transition Metal Electrophiles via Cooperative Catalysis: The Direct Asymmetric α-Allylation of Aryl Acetic Acid Esters

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Supporting Information

ABSTRACT: The direct, catalytic, asymmetric α-functionalization of acyclic esters constitutes a significant challenge in the area of asymmetric catalysis, particularly where the configurational integrity of the products is problematic. Through the unprecedented merger of two independent, yet complementary, catalysis events it has been possible to facilitate the direct asymmetric α-allylation of readily available aryl acetic acid esters. Since enantioselection is determined by the nucleophile, this conceptual approach to cooperative catalysis constitutes a potentially general solution to the direct catalytic asymmetric α-functionalization of acyclic esters.

In cooperative or synergistic catalysis chemical bond formation occurs via the unification of distinct intermediates manufactured by simultaneous yet discrete catalysis events.[1] Attracted by this potentially expansive approach to reaction design, we questioned whether this notion might be harnessed to develop a general solution to the direct, catalytic asymmetric α-functionalization of acyclic esters (Figure 1a). More specifically, we envisioned the union of C1-ammonium enolate nucleophiles and transition-metal electrophiles via two precisely orchestrated and complementary catalysis platforms.[2] Within this nascent framework we describe the direct, asymmetric α-allylation of acyclic aryl acetic acid esters (Figure 1b).

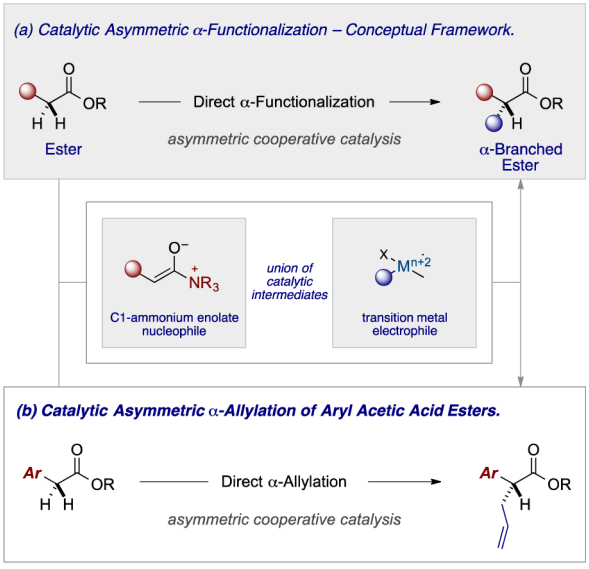

Figure 1. (a) Conceptual framework for the direct asymmetric α-functionalization of esters. (b) This work: the direct α-allylation of aryl acetic acid esters.

Transition-metal-catalyzed allylic alkylation reactions are much lauded, versatile, and now commonplace methods for asymmetric carbon−carbon and carbon−heteroatom bond formation.[3] Adorned with a bewildering array of ligands, numerous low-valent transition metals serve as effective catalysts and direct the trajectory of a wide range of nucleophiles with high levels of regio-, diastereo-, and enantio-control. However, while the catalyst governs electrophile facial selectivity with high fidelity, extending stereoselection to the nucleophilic partner can be more challenging. Prochiral esters are commonly employed but require the derived enolate be stereodefined. Electronically and sterically biased ester pro-nucleophiles[4] are effective, as are stereodefined ester enolate equivalents,[5] but the *direct* employment of linear esters is complicated by the strong bases necessary for their preparation and/or the inevitable production of enolate isomers.[6] Cognizant of this, we considered C1-ammonium enolates as nonstabilized, acyclic ester enolate equivalents.[7] These can be generated from simple, activated carboxylic acid derivatives, exist as single isomers, and engage in enantioselective carbon−carbon, carbon−heteroatom and carbon−halogen bond formation with standard electrophiles under the escort of simple nucleophilic tertiary amine catalysts. Furthermore, their generation does not require strong bases, thereby preserving the integrity of enolizable stereogenic centers.[8] However, critical to their union with any π-(allyl)metal electrophile is the identification of a turnover mechanism for the nucleophilic catalyst.

In typical reactions implicating C1-ammonium enolates discrete ion pairs are not formed and catalyst turnover occurs by intramolecular attack of a proximal nucleophile on an intermediate acyl ammonium ion.[7] In a cooperative regimen, successful turnover would demand intermolecular attack by an exogenous nucleophile. The feasibility of this finds support in recent reports. In a seminal study, Scheidt and co-workers revealed the propensity of 4-nitrophenolate to act as a rebound nucleophile and effect turnover of *N*-heterocyclic carbene catalysts via phenolysis of intermediate acyl azolium ions.[9] In

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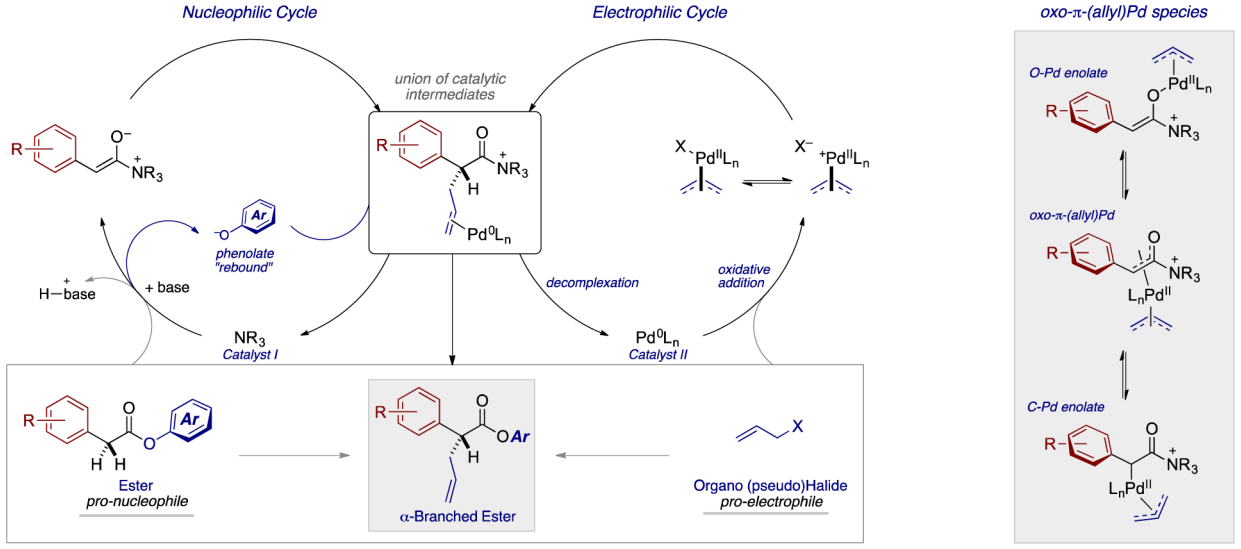
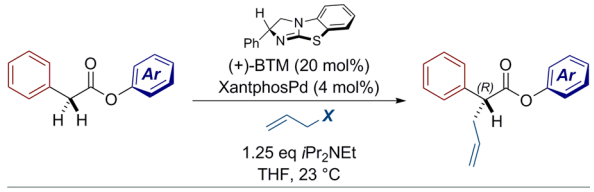
Scheme 1. Postulated Cooperative Catalysis Mechanism



the only report of an analogous process implicating acyl ammonium ion intermediates, Smith and co-workers harnessed Scheidt's 4-nitrophenolate rebound in their generation and asymmetric [2,3]-sigmatropic rearrangement of C1-ammonium enolates.[10,11] In considering these, we envisioned a plausible mechanistic scenario where C1-ammonium enolates and π-(allyl)palladium electrophiles unite via cooperative catalysis, and turnover of the nucleophilic catalyst occurs via phenolate rebound (Scheme 1). Additionally, the plenitude of available chiral nucleophilic tertiary amine catalysts raised the prospect of developing an enantioselective process.

Our initial efforts focused on the structure of the aryl ester and nature of the allyl nucleofuge (Table 1). Employing XantphosPd[12] and (+)-benzotetramisole[13] as transition metal and nucleophilic catalysts, respectively, the α-allylation of *p*-nitrophenyl ester **1** was utilized as a benchmark transformation[14] (entries 1−7). While the allylation product was obtained regardless of the leaving group employed, the degree of enantioselectivity varied markedly. Moving from allylic esters (entries 1 and 2) to allylic phosphates and allylic carbonates (entries 3−6) resulted in higher yields and enhanced levels of (*R*)-enantioenrichment. In response to this initial trend we increased the nucleofugality of the leaving group. While allyl chloride provided the desired product in modest yield and enantioselectivity (entry 7), allyl mesylate resulted in 62% yield (42% isolated)[15] and 92% ee (entry 8). Unfortunately, material loss during isolation could not be suppressed and neither the yield nor reaction time optimized further. We therefore undertook a survey of aryl esters to assess their capacity as Scheidt-type rebound nucleophiles (entries 9−12). Of these, fluorinated phenyl esters **3** and **4** proved to be exceptionally effective. Furthermore, and in contrast to the 4-nitrophenyl esters, greatly reduced reaction times were required and chromatographic isolation of the product esters was trivial and efficient. We selected pentafluorophenyl esters (such as **4**) for further study as they are established and versatile acyl donors and exhibit useful hydrolytic stability.[16] Having established effective conditions,[17] a variety of aryl acetic acid pentafluorophenyl esters was evaluated (Table 2, X = OMs). There appears to be little sensitivity to changes in the electronics of the arene; fluoride, chloride, and bromide substituents are tolerated (**15**, **9**, and **11**), as is ortho substitution. Of further synthetic utility is the allylation of indole-containing NSAID-Pfp ester, **17**. Unfortunately, efforts to extend the scope of the partner mesylate were unsuccessful.

Table 1. Optimization Studies



Entry[a]	Ar	X	Time [h]	Yield [%][b,c]	ee [%][d]
1	**1**	OAc	72	50	3
2		OPiv	72	56	5
3		$OP(O)(OEt)_2$	72	20	77
4		$OP(O)(OPh)_2$	72	43	84
5		OCO_2iBu	72	80[e]	53
6		OCO_2tBu	72	85	52
7		Cl	72	40	38
8		OMs	72	62 (42)	92
9	**2**	OMs	72	37	40
10	**3**	OMs	6	85 (75)	94
11	**4**	OMs	6	91 (88)	92
12	**5**	OMs	72	0	--
13[f]	**4**	OMs	6	0	--
14[g]	**4**	OMs	6	0	--

[a]Reactions performed on a 0.1 mmol scale. [b]Yields determined by ^1H NMR comparison with an internal standard (1,2,4,5-tetramethylbenzene). [c]Isolated yields in parentheses. [d]Determined by chiral HPLC analysis. [e]12:1 mixture of aryl:iBu esters. [f]No (+)-BTM. [g]No XantphosPd.

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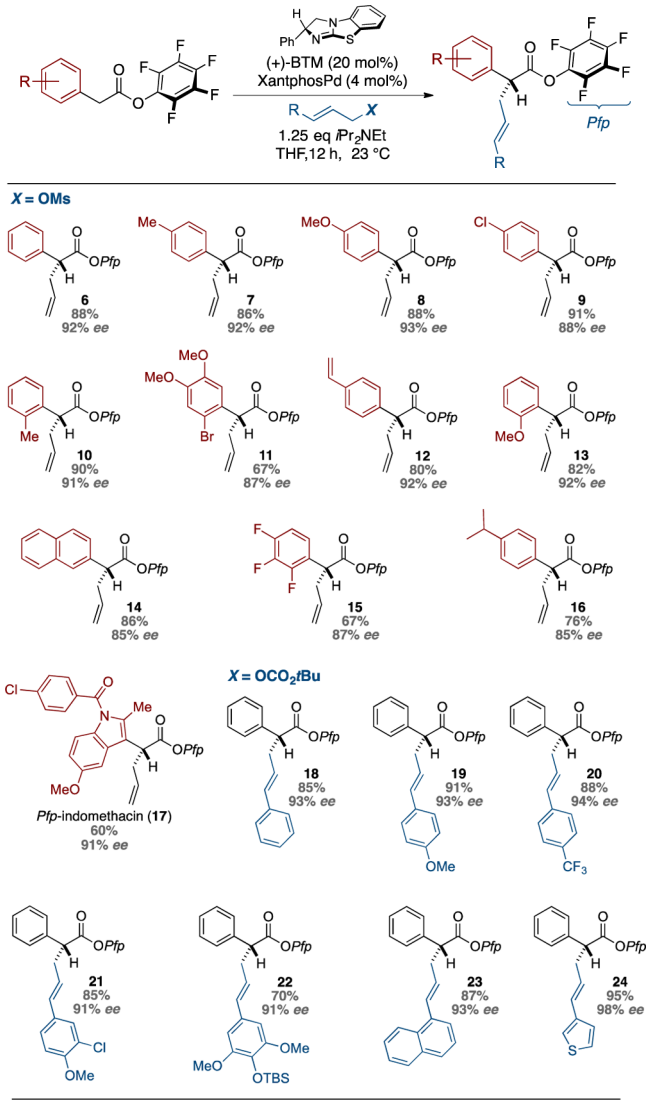
Table 2. Substrate Scope[a]



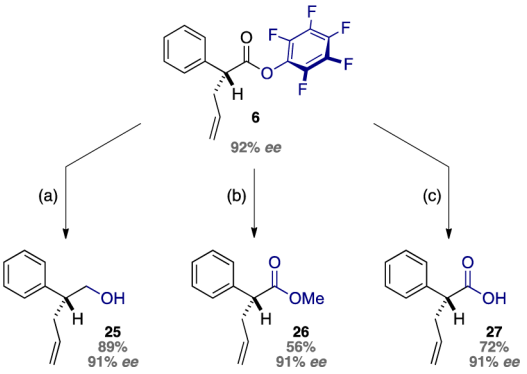
[a]All yields refer to isolated yields following silica gel chromatography. Enantiomeric excess was determined by chiral HPLC in comparison to the racemate.

A comprehensive reassessment of the leaving group revealed cinnamyl *tert*-butylcarbonates to be particularly effective reaction partners (Table 2, X = OCO_2tBu).[18] In each case the linear product was obtained as the *E*-alkene isomer in excellent isolated yield and enantiomeric excess. Moreover, electronic modulation was again inconsequential (**18**−**22**), and the arene structure could be varied (**23** and **24**).

The synthetic utility of this process is further enhanced by the activated nature of the product esters. Despite their configurational sensitivity, their transformation to standard products could be accomplished in high yields and with little to no erosion of enantiopurity (Scheme 2).

The mechanistic scenario we have posited provides useful didactic guidelines for further development (Scheme 1); however, the precise manner in which the two catalytic events integrate is unknown. Nonetheless, it is tempting to speculate on the intermediacy of enolate-ligated π-(allyl)Pd(II) species[19−21] (Scheme 1, right). In addition to a well-ordered transition state this offers a possible explanation for the critical influence of the nucleofuge (X^-) where affinity for Pd(II) might well be determinant. While mechanistic clarification must await further study, the sense of enantioselectivity observed can nevertheless be rationalized by a tentative induction model (Figure 2).[10] In a highly pre-organized (*Z*)-C1-ammonium enolate incorporating a stabilizing and rigidifying $n_O \rightarrow \sigma_{C-S}^*$ electrostatic interaction (**28**),[22] facial addition is governed by the pendant phenyl group. Accordingly, the electrophile is directed to the distal face furnishing the (*R*)-configured acyl ammonium ions (**29**) and thence ester products.

Scheme 2. Transformation of Products[a]



[a]Conditions: (a) $LiAlH_4$, Et_2O, rt, 2 h; (b) HCl/MeOH, 60 °C, 36 h; (c) Me_3SnOH, 1,2-DCE, 70 °C, 12 h.

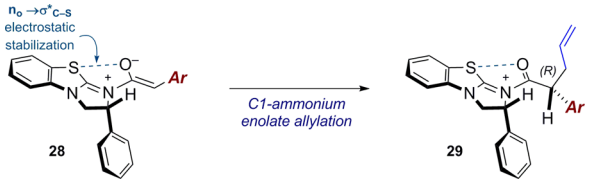


Figure 2. Stereochemical model.

In conclusion, we have developed a novel cooperative catalysis-based method for the direct asymmetric α-allylation of acyclic esters. Notably, this protocol occurs at room temperature, does not require the prior preparation of a stereodefined ester enolate, nor does it require strong bases that compromise the optical purity of the products. Furthermore, and in contrast to common transition-metal-catalyzed approaches, stereocontrol is provided by the nucleophilic catalyst rather than by metal-based ligand frameworks. On a fundamental level this work constitutes the first example of C1-ammonium enolates being united with catalytically generated transition-metal electrophiles and emulates nature's ubiquitous employment of simultaneous yet distinct catalysis events to effect chemical transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01694.

Experimental details and data (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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