Communication

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

Kevin J. Schwarz, Jessica L. Amos, James Cullen Klein, Dung T. Do, and Thomas N. Snaddon J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/jacs.6b01694 • Publication Date (Web): 30 Mar 2016 Downloaded from http://pubs.acs.org on March 31, 2016

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036 Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

7 8

9

10 11 12

13 14

15 16 17

18 19

20

21

22

23

24

25

26

27

28

29

30

31 32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59 60

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

Kevin J. Schwarz, Jessica L. Amos, J. Cullen Klein, Dung T. Do, Thomas N. Snaddon*

Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Bloomington, Indiana 47405, United States.

Supporting Information Placeholder

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, inexpensive 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).

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 nucleo-



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.

philic partner can be more challenging. Prochiral esters are commonly employed but require the derived enolate be stereodefined. Electronically and sterically biased ester pro-nucleophiles⁴ 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 non-stabilized, 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

Scheme 1. Postulated cooperative catalysis mechanism.



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 the only report of an analogous process implicating acyl ammonium ion intermediates, Smith and coworkers 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 XantphosPd¹² and (+)-benzotetramisole¹³ as transition metal and nucleophilic catalysts, respectively; the α -allylation of *p*-nitrophenyl ester **1** was utilized as a benchmark transformation¹⁴ (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 phosphonates 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

Table 1. Optimization Studies.



^aReactions performed on a 0.1 mmol scale. ^bYields determined by ¹H-NMR comparison with an internal standard (1,2,4,5tetramethylbenzene). ^cIsolated yields in parentheses. ^dDetermined by chiral HPLC analysis. e12:1 mixture of aryl:iBu esters. ^fNo (+)-BTM. ^gNo XantphosPd.

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

Pd

NR₃

1

2

3

4

5

6

7

8

9

10

11

12

13

14 15

20

21

22

23 24

25

26

27

28 29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

Table 2. Substrate Scope.



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

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 conditions¹⁷ 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 mesvlate were unsuccessful. A comprehensive reassessment of the leaving group revealed cinnamyl *tert*-butylcarbonates to be particularly effective reaction partners (Table 2, $X = OCO_2 tBu$).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).

Scheme 2. Transformation of products.



Conditions: (a) LiAlH₄, Et₂O, r.t., 2 h; (b) HCl/MeOH, 60 °C, 36 h; (c) Me₃SnOH, 1,2-DCE, 70 °C, 12 h.

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) species¹⁹⁻²¹ (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)-C1ammonium enolate incorporating a stabilizing and rigidifying $n_0 \rightarrow \sigma^*_{C-S}$ electrostatic interaction (28),²² facial addition is governed by the pendant phenyl group. Acco-



Figure 2. Stereochemical model.

rdingly, the electrophile is directed to the distal face furnishing the (R)-configured acyl ammonium ions (29), and thence ester products.

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.

Experimental procedures and characterization data (PDF).

AUTHOR INFORMATION

Corresponding Author

*tsnaddon@indiana.edu

Notes

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59 60 The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge generous financial support from Indiana University. This manuscript is dedicated to Professors Philip J. Kocienski, Alois Fürstner and Steven V. Ley.

REFERENCES

(1) For selected reviews articulating this concept, see: (a) Cooperative Catalysis: Designing Efficient Catalysts for Synthesis; Peters, R. Ed.; Wiley-VCH: Weinheim, 2015; (b) Deng, Y.; Kumar, S.; Wang, H. Chem. Commun. 2014, 50, 4272–4284; (c) Du, Z.; Shao, Z. Chem. Soc. Rev. 2013, 42, 1337–1378; (d) Allen, A. E.; MacMillan, D. W. C. Chem. Sci. 2012, 3, 633–658; (e) Ma, J.-A.; Carhard, D. Angew. Chem., Int. Ed. 2004, 43, 4566–4583.

(2) For selected examples of merging organocatalysis-derived nucleophiles with π -(allyl)metal electrophiles, see: (a) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363–14367; (b) Zhou, H.; Zhang, L.; Xu, C.; Luo, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 12645–12648; (c) Liu, K.; Hovey, T.; Scheidt, K. A. *Chem. Sci.* **2014**, *5*, 4026–4031; (d) Terret, J. A.; Clift, M. D.; MacMillan, D. W. C. J. Am. Chem. Soc. **2014**, *136*, 6858–6861; (e) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. J. Am. Chem. Soc. **2014**, *136*, 3020–3023; (f) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. J. Am. Chem. Soc. **2014**, *136*, 13606–13609; (g) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Science. **2013**, *340*, 1065–1068; (h) Bihelovic, F.; Matovic, R.;

Vulovic, B.; Saicic, R. N. Org. Lett. **2007**, *9*, 5063–5066; (i) Ibrahem, I.; Cordova, A. Angew. Chem. Int. Ed. **2006**, *45*, 1952–1956.

(3) For excellent reviews, see: (a) Weaver, J. D.; Recio, III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846–1913; (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944; (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.

(4) For selected recent examples employing β-ketoesters, see (a) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. J. Am. Chem. Soc. 2013, 135, 17298–17301; (b) Liu, W.-B.; Reeves, C. M.; Virgil, S. M.; Stoltz, B. M. J. Am. Chem. Soc. 2013, 135, 10626–10629; (c) Kuwano, R.; Uchida, K.-i.; Ito, Y. Org. Lett. 2003, 5, 2177–2179; (d) Trost, B. M.; Sacchi, K. L.; Schroeder, G. M.; Asakawa, N. Org. Lett. 2002, 4, 3427–3430. For selected recent examples employing cyclic enolates, see (e) Craig, II, R. A.; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. H.; Stoltz, B. M. Org. Lett. 2015, 17, 5160–5163; (f) Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk, K. N.; Stoltz, B. M. Org. Lett. 2015, 17, 1082–1985; (g) Trost, B. M.; Ariza, X. J. Am. Chem. Soc. 1999, 121, 10727–10737.

(5) (a) Trost, B. M.; Michaelis, D. J.; Charpentier, J.; Xu, J. Angew. Chem., Int. Ed. **2012**, *51*, 204–208; (b) Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K. J. Am. Chem. Soc. **2010**, *132*, 8915–8917.

(6) (a) Ariyarathna, Y.; Tunge, J. A. Org. Biomol. Chem. 2014, 12, 8386–8389; (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. Org. Lett. 2001, 3, 3329–3331.

(7) For reviews, see: (a) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214–6226; (b) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771–6803.

(8) (a) Kita, Y.; Numajiri, Y.; Okamoto, B. M.; *Tetrahedron*, **2015**, *71*, 6349–6353; (b) Korch, K. M.; Eidamnshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M.; *Angew. Chem., Int. Ed.* **2015**, *54*, 179–183.

(9) Kawanka, Y.; Phillips, E. M.; Scheidt, K. A. J. Am. Chem. Soc. 2009, 131, 18028–18029.

(10) West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. J. Am. Chem. Soc. 2014, 136, 4476–4479.

(11) For other acyl ammonium phenolysis, see: (a) Lee, S. Y.; Neufeind, S.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 8899–8902; (b) Dogo-Isonagie, C.; Bekele, T.; France, S.; Wolfer, J.; Weatherwax, A.; Taggi, A. E.; Paull, D. H.; Dudding, T.; Lectka, T. *Eur. J. Org. Chem.* **2007**, 1091–1100.

(12) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Chem. Sci. 2013, 4, 916–920.

(13) A range of common nucleophilic amine catalysts was surveyed and isothioureas proved uniquely effective (see supporting information for details). Smith and co-workers have noted similar observations, see Ref (10).

(14) Andrus, M. B.; Harper, K. C.; Christiansen, M. A.; Binkley, M. A. *Tetrahedron Lett.* **2009**, *50*, 4541–4544; (b) Stivala, C. E.; Zakarian, A. J. Am. Chem. Soc. **2011**, *133*, 11936–11939.

(15) For similar lower than expected isolated yields. See ref 11.

(16) (a) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1996**, *37*, 4915–4918; (b) Green, M.; Berman, J. *Tetrahedron Lett.* **1990**, *31*, 5851–5852; (c) Atherton, E.; Cameron, L. R.; Sheppard, R. C. *Tetrahedron* **1988**, *44*, 843–857; (d) Kisfaludy, L.; Roberts, J. E.; Johnson, R. H.; Mayers, G. L.; Kovacs, J. J. Org. Chem. **1970**, *35*, 3563–3565.

(17) Both catalysts are required (Table 1, entries 14 and 15).

(18) See supporting information for details.

(19) For Pd(II)-metallated C1-ammonium enolates, see: (a) Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* **2011**, *133*, 7536–7546; (b) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17085–17094.

(20) (a) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. Organometallics **1999**, *18*, 5571–5576, and references cited therein.

(21) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. J. Am. Chem. Soc. **2012**, *134*, 19050–19060.

(22) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. Org. Lett. 2012, 14, 3288–3291.

Page 5 of 5

Journal of the American Chemical Society

	asymmetric cooperative catalysis ── Direct a-Allylation ──► 19 examples 85–98% ee		
 Esters	α -Branched Esters		