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Enantioselective α-Benzylation of Acyclic Esters Using π-Extended Electrophiles.

Kevin J. Schwarz, Chao Yang, James W. B. Fyfe and Thomas N. Snaddon[a]

Dedicated to Dr. Henrik Teller

ABSTRACT: The first asymmetric cooperative Lewis base/Pd catalyzed benzylic alkylation of acyclic esters is reported. This reaction proceeds via stereo-defined C1-ammonium enolate nucleophiles and critical to its success was the identification of benzylic phosphate electrophiles, which were uniquely reactive. Alkylated products are obtained with very high levels of enantioselectivity and this method has been applied toward the synthesis of the thrombin inhibitor DX-9065a.

Enantioselective Pd-catalyzed allylic alkylation reactions are amongst the most versatile and robust methods for the construction of C(sp^3)–C(sp^3) bonds.[1] Under the action of a suitable Pd catalyst, carbogenic nucleophiles react efficiently with allylic electrophiles. These reactions typically proceed via cationic π-(allyl)$Pd^{II}L_n$ species, the reactivity and stereocontrol elements of which can be readily tuned by the supporting ligands. Despite possessing iso-structural and iso-electronic characteristics asymmetric Pd-catalyzed *benzylic* alkylation reactions using enolate nucleophiles are far less common.[2] This is attributable, in part, to the difficulty in forming Pd^0/arene complexes and the relatively high energy required for dearomatizing ionization/oxidative addition (Figure 1a).

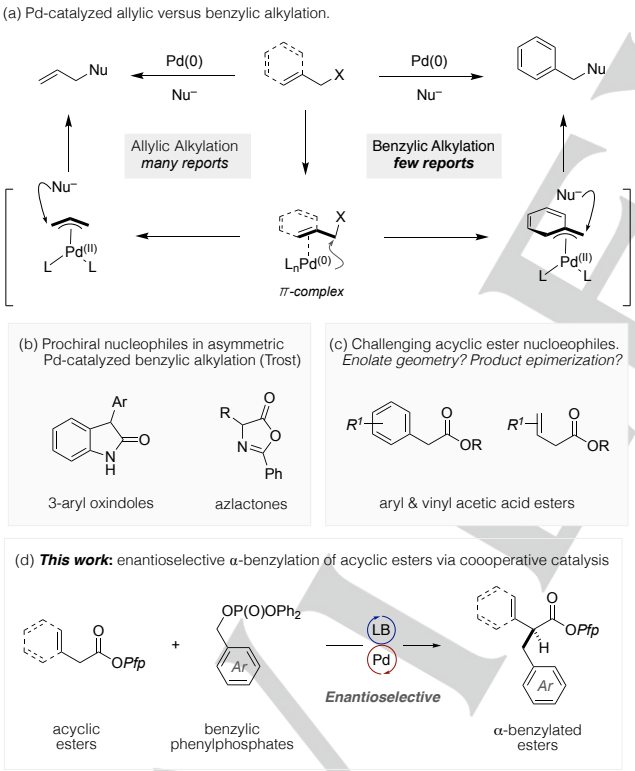
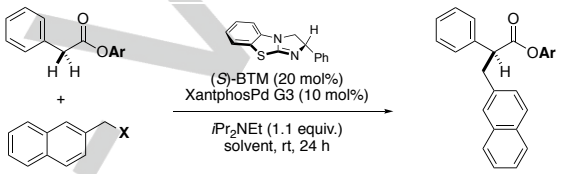


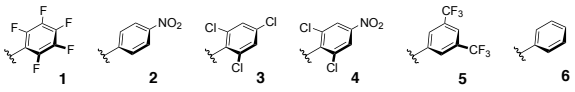
Figure 1. (a) Pd-Catalyzed allylic versus benzylic alkylation; (b) Competent prochiral nucleophiles in asymmetric Pd-catalyzed benzylation; (c) Challenging acyclic ester nucleophiles; (d) This work: direct enantioselective α-benzylation.

Table 1. Optimization Studies.



Entry[a]	X	Ar	Solvent	Yield [%][b,c]	er[d]
1	OTs	1	THF	0	--
2	OAc	1	THF	0	--
3	OCO_2tBu	1	THF	0	--
4	$OP(O)(OEt)_2$	1	THF	5	--
5	$OP(O)(OPh)_2$	1	THF	68	97:3
6	$OP(O)(OPh)_2$	1	Dioxane	60	93:7
7	$OP(O)(OPh)_2$	1	CH_2Cl_2	40	89:11
8	$OP(O)(OPh)_2$	1	Toluene	85 (81)	99:1
9	$OP(O)(OPh)_2$	2	Toluene	82	94:6
10	$OP(O)(OPh)_2$	3	Toluene	21	--
11	$OP(O)(OPh)_2$	4	Toluene	0	--
12	$OP(O)(OPh)_2$	5	Toluene	75	99:1
13	$OP(O)(OPh)_2$	6	Toluene	0	--

Ar =



[a] Reactions performed on a 0.1 mmol scale. [b] Yields determined by ^{1}H NMR by comparison with an internal standard (1,2,4,5-tetramethylbenzene). [c] Isolated yield in parentheses. [d] Determined by chiral HPLC analysis.

Outstanding studies by Fiaud, Kwano and Tunge provide some resolution to this restriction;[3] however, the generation of enantioenriched products remains a major challenge. Focusing on the generation of stereochemistry at the electrophilic carbon, noteworthy contributions from Fiaud and Hirano/Murai have described the use of secondary benzyl electrophiles and proceed via partial kinetic resolution or dynamic kinetic asymmetric transformation (DYKAT), respectively.[4,5] To address stereochemical induction at the nucleophilic carbon, Trost and Czabaniuk reported the highly enantioselective benzylation of cyclic prochiral azlactone and 3-aryl-oxindole nucleophiles using primary benzylic carbonates and phosphates (Figure 1b).[6] Although few in number, these remain the most

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effective Pd-catalyzed benzylic alkylation methods available.[7] So far the use of acyclic ester nucleophiles has not been described despite the clear utility of the products (Figure 1c).

In response to long-standing challenges associated with the use of acyclic prochiral nucleophiles in asymmetric transition metal catalyzed transformations, our laboratory has embraced cooperative Lewis base/transition metal catalysis as a general design principle.[8] Proceeding via C1-ammonium enolate nucleophiles, this construct results in a general reaction template that accommodates a variety of transition metal catalyzed processes.[9] Herein, we further advance our cooperative framework by demonstrating, for the first time, that C1-ammonium enolates effectively react with putative cationic π-(benzyl)Pd^{II} electrophiles resulting in the highly enantioselective benzylic alkylation of aryl and vinyl acetic acid esters using π-extended benzylic phosphate electrophiles (Figure 1d).

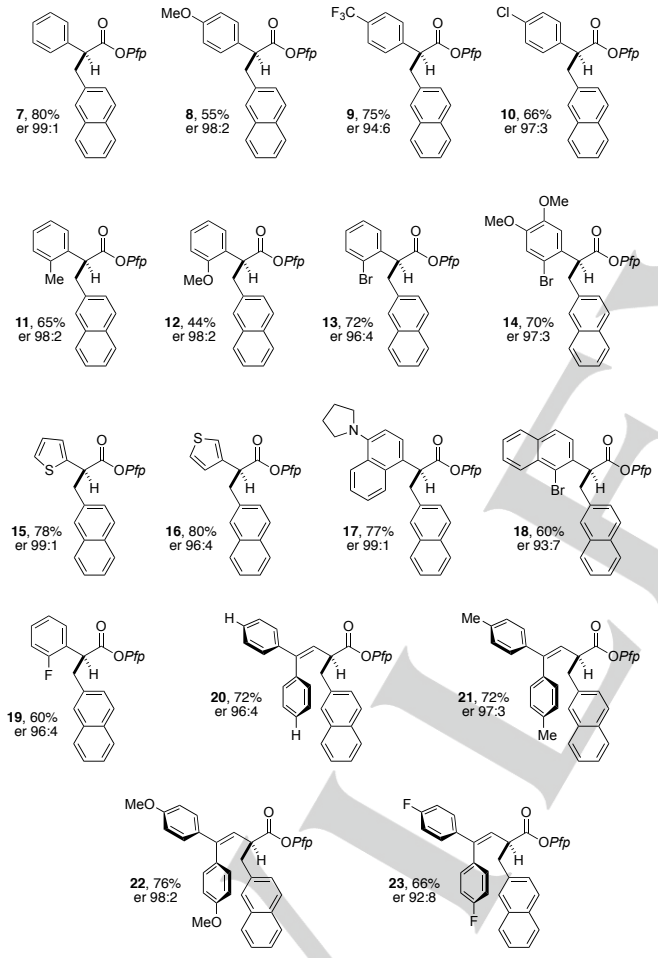


Figure 2. Nucleophile Scope: [a] Reactions performed on a 0.1 mmol scale. Yields are isolated following chromatography. *er* Determined by chiral HPLC analysis.

During their seminal benzylation studies, Trost and Czabaniuk described the critical role the nucleofuge plays on both the facility of Pd^0 oxidative addition and the obtained enantioselectivity.[6] Within our cooperative catalysis framework we have also observed the drastic effect the nucleofuge plays in enantioselection.[8] Mindful of these observations we surveyed a range of activated 2-naphthyl alcohol derivatives (Table 1).

Employing benzotetramisole (BTM)[10,11] as the Lewis base catalyst and Buchwald's XantphosPd G3 precatalyst[12] we quickly identified diphenyl phosphate as the only competent nucleofuge (Entries 1–5), which furnished the desire product in high yield and excellent enantioselectivity (68%, er 97:3). Further assessment of the solvent identified toluene which gave the product in an enhanced 85% yield and er 99:1. Finally, evaluation of various electron-deficient phenyl esters (**2**–**5**) (Entries 9–12) offered no improvement, although ester **5** did function with notable efficiency (Entry 12). Phenyl ester **6** was ineffective (Entry 13).[13]

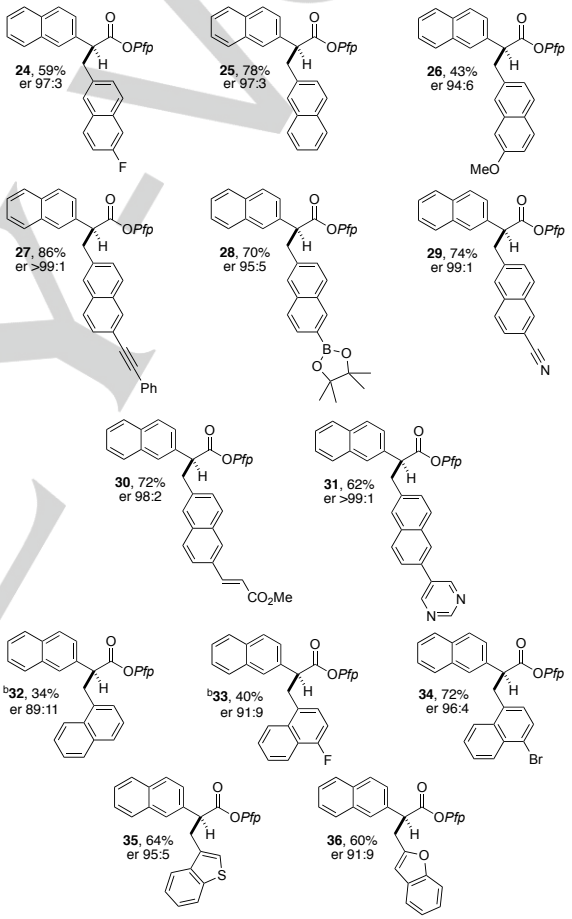
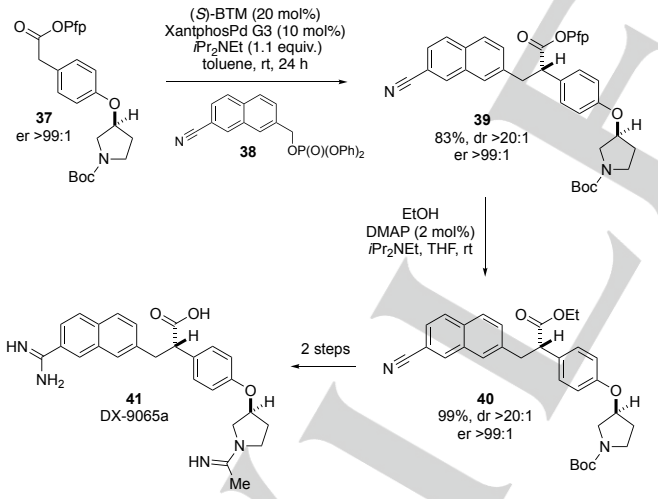


Figure 3. Electrophile Scope: [a] Reactions performed on a 0.1 mmol scale. Yields are isolated following chromatography. *er* Determined by chiral HPLC analysis. [b] isolated as corresponding benzylamide (see SI for details).

With an optimized procedure in hand, we proceeded to evaluate the scope of phenyl acetic Pfp-ester nucleophiles (Figure 2). As expected a wide variety of aryl acetic esters performed well and gave products with excellent levels of enantioselectivity. Notable examples include tolerance of *o*-aryl bromides (**13** and **14**), the performance of 2- and 3-thiophene derived esters (**15** and **16**), and the facility with which arene-rich systems can be

constructed (**20**–**23**). Evaluation of 2-naphthyl electrophile scope (Figure 3) revealed the tolerance of acetylene units (**27**), pinacolboronic esters (**28**), nitriles (**29**), acrylates (**30**) and Lewis basic *N*-heterocycles (**31**). Extension to 1-naphthyl electrophiles (**32**–**34**) as well as regioisomeric benzothiophene (**35**) and benzofuran (**36**) heterobenzylic electrophiles was also possible.[14] While π-extended electrophiles functioned effectively, simple monocyclic benzylic phosphates are unreactive, presumably due to the aforementioned energy required for dearomatization.[2-6] Pfp-esters derived from alkyl acetic acids are also unreactive within this cooperative catalysis framework.

Our interest in this process stems not only from the well-documented challenges associated with enantioselective catalysis via cationic π-(benzyl)Pd intermediates, but also from the potential of such reactions to address the synthesis of therapeutically-relevant chiral molecules. Here we demonstrate the utility of this method toward the synthesis of the thrombin inhibitor DX-9065A (**41**),[15] a selective inhibitor of the coagulant enzyme activated factor X (FXa).[16] Ethyl ester **40** is a key intermediate *en route* to **41** and was previously prepared as a 1:1 diastereomeric mixture at the ester-bearing stereocenter; crystallization provided **41** as a single diastereomer.[14] We envisioned the stereocontrolled preparation of **39** (and thence **40**) using the method described here. In the event, direct alkylation of ester **37** with benzylic phosphate **38** gave **39** in 83% isolated yield as a single diastereomer demonstrating complete catalyst-control over stereoinduction (Scheme 1). Thereafter, transesterification gave the key ethyl ester **40** in quantitative yield.



Scheme 1. Synthesis of DX-9065a.

In conclusion, we have demonstrated the first example of an enantioselective Pd-catalyzed benzylic alkylation of acyclic ester nucleophiles. Critical to the success of this reaction was (i) identification of the uniquely effective phosphate nucleofuge, and (ii) the cooperative action of a Lewis base catalyst, which governs the *in situ* production of stereo-defined C1-ammonium enolate nucleophiles as well as the enantioselectivity of the reaction. This is complementary to the ligand-centered enantiocontrol typical of Pd-catalysis, and further demonstrates the potential of cooperative catalysis to address challenges in reactivity and stereocontrol that are be beyond single catalysts. Our current efforts are directed toward the union of monocyclic benzyl electrophiles with C1-ammonium enolates and will be reported in due course.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: benzylation • palladium • cooperative catalysis • Lewis base • enantioselective

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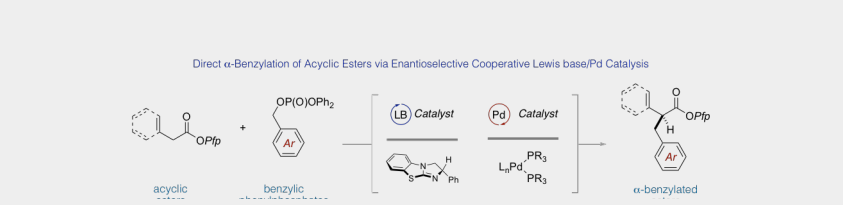

Cooperate to Benzylate!: Cooperative catalysis enables the direct enantioselective α-benzylation of aryl and vinyl acetic acid esters using π-extended benzylic electrophiles. Critical to the successful development of this method was the identification of diphenylphosphate as a uniquely effective nucleofuge, which permits oxidative addition of Pd(0). This method has been applied toward the synthesis of thrombin inhibitor DX-9065a.

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