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

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Abstract

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

Keywords

benzylation; cooperative catalysis; enantioselectivity; Lewis bases; palladium

Enantioselective palladium-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 isostructural and isoelectronic 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 1 a).

Outstanding studies by the groups of Fiaud, Kwano, and Tunge provided 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 atom, noteworthy contributions from Fiaud and Hirano/Murai have described the use of secondary benzyl electrophiles in reactions that proceed by partial kinetic resolution or by a dynamic kinetic asymmetric transformation (DYKAT), respectively.[4,5] To address stereochemical induction at the nucleophilic carbon atom, Trost and Czabaniuk reported the highly enantioselective benzylation of cyclic prochiral azlactone and 3-aryl oxindole nucleophiles using primary benzylic carbonates and phosphates (Figure 1 b).[6] Although few in number,

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Conflict of interest

The authors declare no conflict of interest.

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

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, enabling the highly enantioselective benzylic alkylation of aryl- and alkenylacetic acid esters with π-extended benzylic phosphate electrophiles (Figure 1 d).

During their seminal benzylation studies, Trost and Czabaniuk described the critical role of the nucleofuge in determining 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 that 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 diphenylphosphate as the only competent nucleofuge (entries 1–5), which furnished the desired 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 aryl 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]

With an optimized procedure in hand, we proceeded to evaluate the scope of arylacetic Pfp ester nucleophiles (Figure 2). As expected, a wide variety of arylacetic esters performed well and gave the corresponding products with excellent levels of enantioselectivity. Notable examples include the tolerance of *o*-bromophenyl moieties (**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 the electrophile scope using the Pfp ester of 2-naphthylacetic acid (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] Whereas π-extended electrophiles functioned effectively, simple monocyclic benzylic phosphates were unreactive, presumably owing to the aforementioned energy required for dearomatization.[2–6] Pfp esters derived from alkylacetic 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 towards 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.[15] 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.

In conclusion, we have demonstrated the first enantioselective palladium-catalyzed benzylic alkylation of acyclic ester nucleophiles. Critical to the success of this reaction was 1) the identification of the uniquely effective phosphate nucleofuge and 2) the cooperative action of a Lewis base catalyst, which governs the in situ production of stereodefined C1-ammonium enolate nucleophiles as well as the enantioelectivity of the reaction. This is complementary to the ligand-centered enantiocontrol typical of palladium catalysis, and further demonstrates the potential of cooperative catalysis to address challenges in reactivity and stereocontrol that are beyond single catalysts. Our current efforts are directed towards the union of monocyclic benzyl electrophiles with C1-ammonium enolates and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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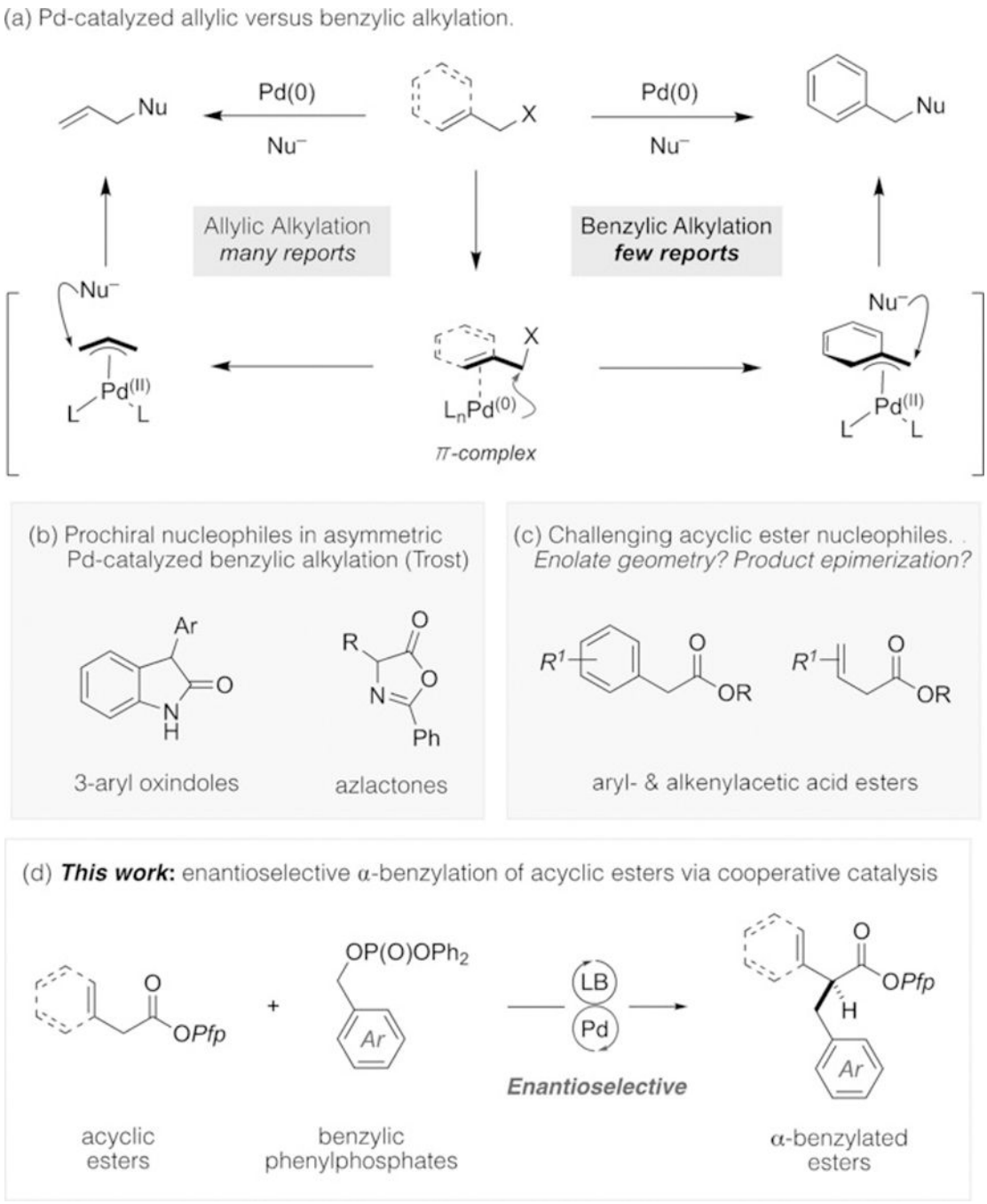


Figure 1.

a) Palladium-catalyzed allylic versus benzylic alkylation. b) Competent prochiral nucleophiles in asymmetric palladium-catalyzed benzylation. c) Challenging acyclic ester nucleophiles. d) This work: Direct enantioselective α-benzylation.

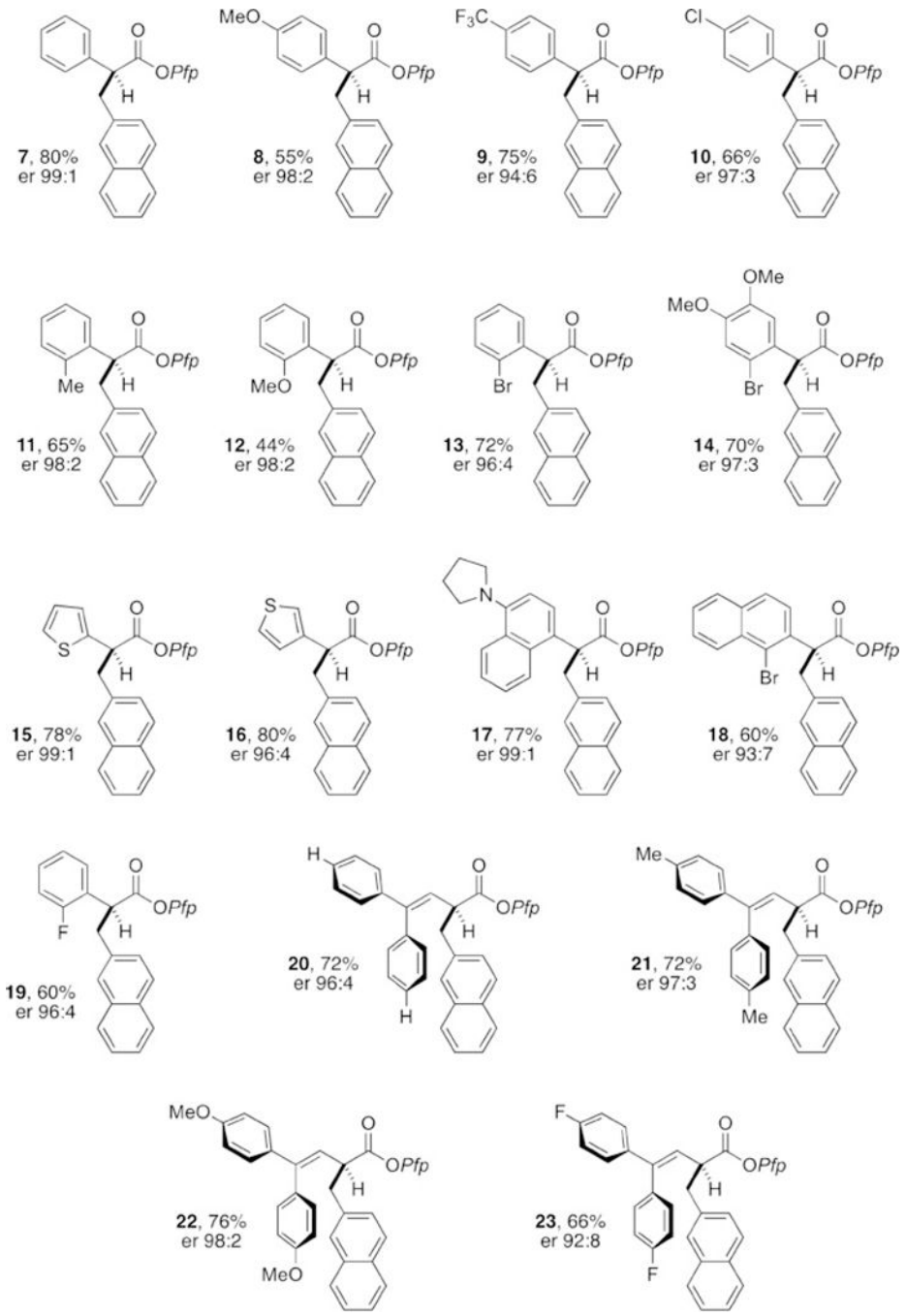


Figure 2.

Nucleophile scope. Reactions performed on 0.1 mmol scale. Yields of isolated produts after purification by column chromatography are given. The er values were determined by HPLC analysis on a chiral stationary phase.

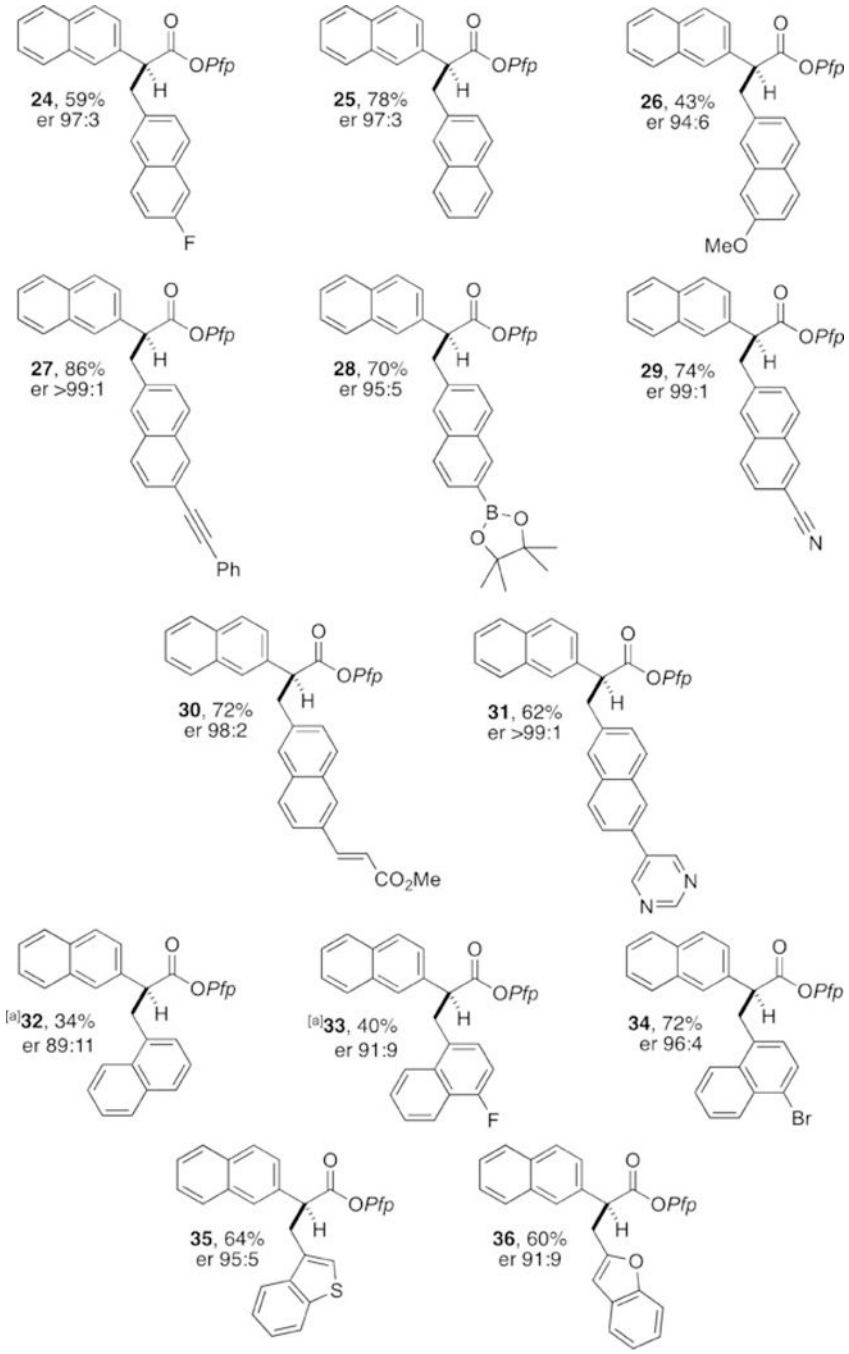
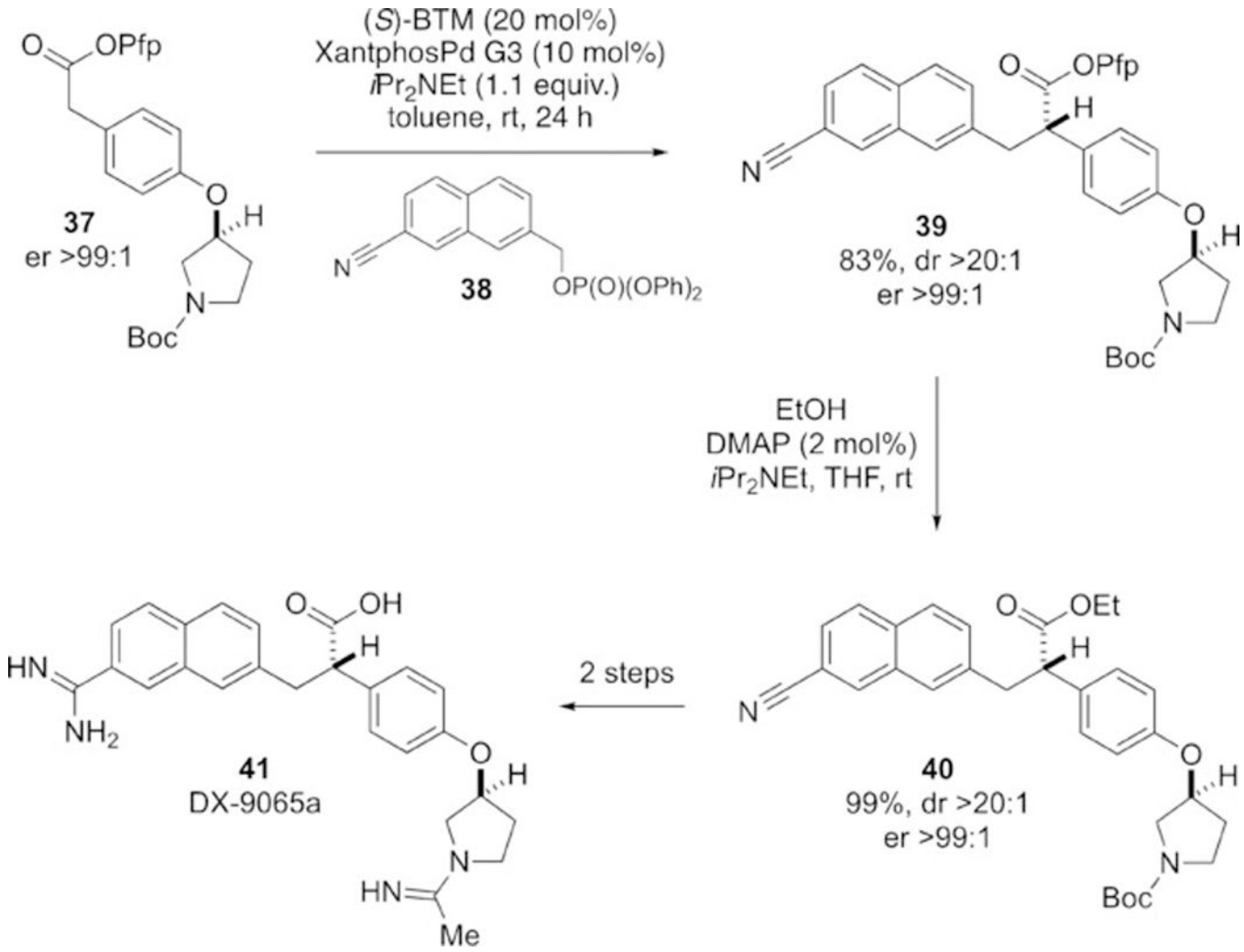


Figure 3.

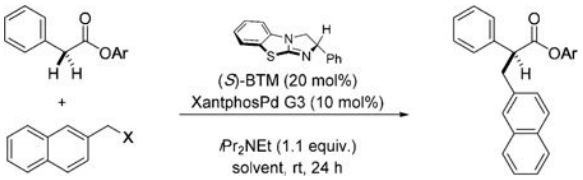
Electrophile scope. Yields of isolated produts after purification by column chromatography are given. The er values were determined by HPLC analysis on a chiral stationary phase. [a] Isolated as the corresponding benzylamide (see the Supporting Information for details).



Scheme 1.
Synthesis of DX-9065a.

Table 1:

Optimization studies.



Entry[a]	X	Ar	Solvent	Yield [%][b]	er[c]
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**	1,4-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	–

[a] Reactions performed on 0.1 mmol scale.

[b] Yields determined by ^1H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard. Yields of isolated products given in parentheses.

[c] Determined by HPLC analysis on a chiral stationary phase.

Ms= methane-sulfonyl, Pfp = pentafluorophenyl.