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Synthesis of α-Heteroaryl Propionic Esters by Palladium-Catalyzed α-Heteroarylation of Silyl Ketene Acetals

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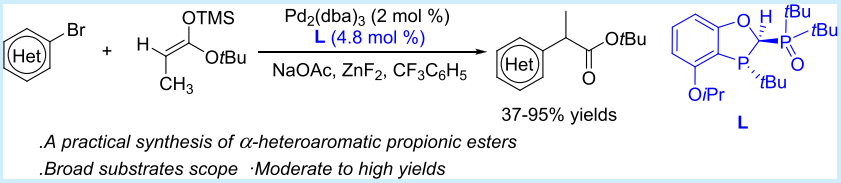
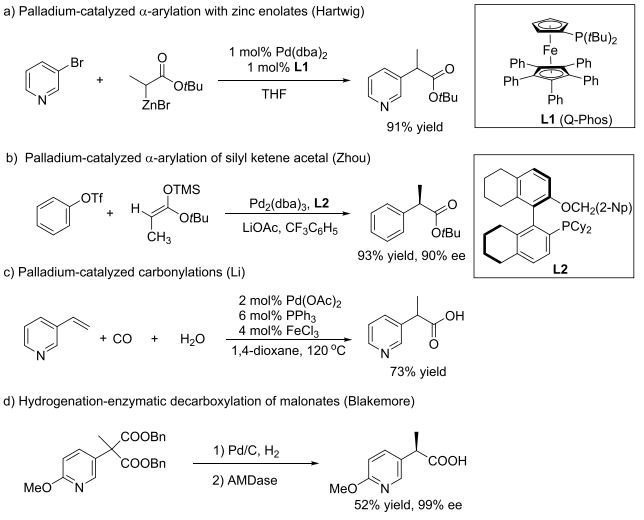


ABSTRACT: A practical and efficient synthesis of α-heteroaryl propionic esters is developed by employing palladium-catalyzed α-heteroarylation of silyl ketene acetals, forming a wide variety of α-heteroaryl propionic esters with various substituents and functionalities in high yields. The success of this transformation is credited to the development of the bulky P,P═O ligand. The method has provided an efficient synthesis of α-heteroaryl propionic acids.

α-Arylalkanoic acids and derivatives are not only synthetically useful building blocks but also common moieties in a number of drug molecules.[1] For instance, this functionality is a key unit of the nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen and naproxen. Likewise, nitrogen-containing heterocycles are valuable building blocks prevalent in many drug molecules,[1] and an efficient synthesis of α-heteroaryl propionic esters remains scarce.[2] In 2003, Hartwig and co-workers described an efficient palladium-catalyzed α-arylation of zinc ester or amide enolates using Q-Phos as the ligand, forming a series of α-aryl propionic esters and amides under neutral conditions (Scheme 1a). Nevertheless, only one example of a heteroaryl halide was reported.[3] Zhou and co-workers later developed an enantioselective protocol of palladium-catalyzed α-arylation of silyl ketene acetals with aryl triflates, albeit with no nitrogen-containing heterocyclic products (Scheme 1b).[4] Li and co-workers prepared a range of α-arylalkanoic acids through palladium-catalyzed carbonylation of vinyl arenes with an iron(III) salt as the additive; however, only limited examples of heteroaryl products were described (Scheme 1c).[5] It should be noted that heteroaryl halides are more accessible and attractive starting materials than the corresponding vinyl heteroaryls. Blakemore and co-workers recently reported a method of preparing enantiopure heteroaromatic propionic acids by employing a telescoped hydrogenolysis−AMDase process of malonates (Scheme 1d).[6] Following a three-step protocol from readily available heteroaromatic halides, this method was demonstrated on 120 g scale. The scope of the reaction was not extensively studied, and the enzymatic effectiveness was highly substrate-specific. Hence, it remains a significant challenge to develop a practical and effective method to prepare α-heteroaryl propionic acids/esters. Herein we report a general and efficient one-step synthesis of α-heteroaryl propionic esters by a palladium-catalyzed α-heteroarylation of silyl ketene acetals.

Scheme 1. α-Arylpropionic Acid Derivatives by Palladium Catalysis



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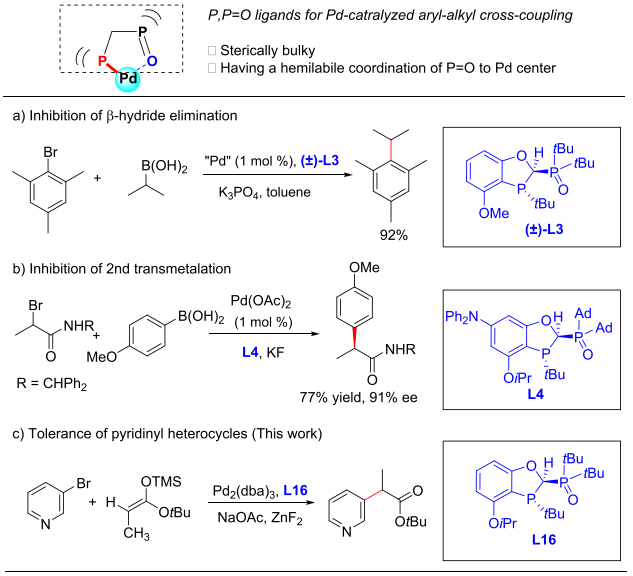
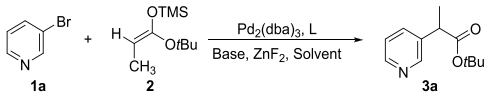
Scheme 2. Design of P,P=O Ligands for Pd-Catalyzed Aryl−Alkyl Cross-Coupling



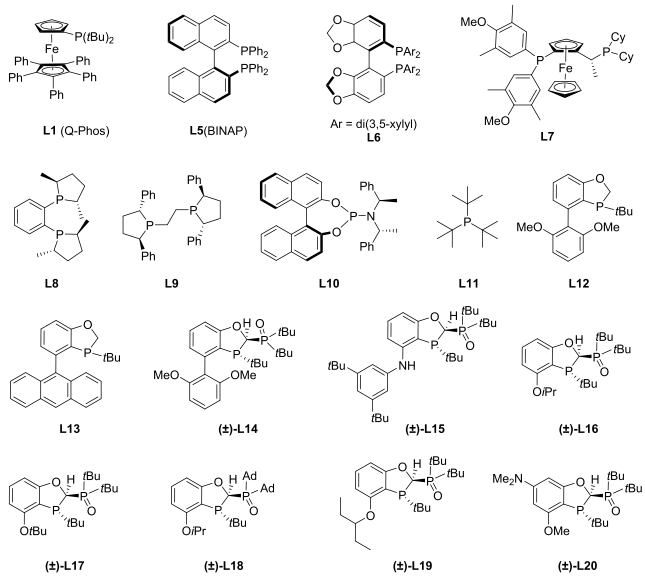
We previously reported efficient aryl−alkyl cross-couplings for the synthesis of chiral/nonchiral building blocks by developing structurally novel and unique P,P=O ligands.[7] By employing a bulky P,P=O ligand **L3**, an efficient cross-coupling between sterically hindered aryl halides and acyclic secondary alkylboronic acids was developed in high yields and excellent chemoselectivities. The role of the P=O moiety was to provide a hemilabile coordination to the Pd center, thereby effectively inhibiting β-hydride elimination (Scheme 2a).[7c] We also realized an enantioselective palladium-catalyzed coupling between α-bromo carboxamides and arylboronic acids for the first time by employing chiral P,P=O ligands with a Pd loading as low as 0.5 mol %. The ligand **L4** was critical for the desired reactivity and enantioselectivity, which effectively inhibited the undesired second transmetalation process (Scheme 2b).[7a] Herein, we detail that the employment of P,P=O ligand **L16** also provides exceptional tolerance for pyridinyl heterocycles in palladium-catalyzed α-heteroarylation (Scheme 2c).

The palladium-catalyzed cross-coupling of 3-bromopyridine (**1a**) and (*E*)-*O*-TMS ketene acetal (**2**) was selected as the model reaction for this study. Reactions were carried out in toluene with NaOAc as the base and ZnF_2 as an additive in the presence of $Pd_2(dba)_3$ (2 mol %) and ligand (4.8 mol %) (Table 1). A number of commercially available bisphosphorus ligands including BINAP (**L5**), DM-SEGPHOS (**L6**), Me-DuPhos (**L8**), and Ph-BPE (**L9**), as well as monophosphorus ligands Q-Phos (**L1**), P(tBu$_3$) (**L11**), BI-DIME (**L12**), and AntPhos (**L13**),[8] were employed for this transformation, and all failed to provide the desired coupling product **3a** (entries

Table 1. Palladium-Catalyzed α-Heteroarylation between 3-Bromopyridine (1a) and (*E*)-*O*-TMS Ketene Acetal (2)



entries[a]	ligand	base	solvent	yield of **3a** (%)
1	**L1**	NaOAc	toluene	0
2	**L5**	NaOAc	toluene	0
3	**L6**	NaOAc	toluene	0
4	**L7**	NaOAc	toluene	0
5	**L8**	NaOAc	toluene	0
6	**L9**	NaOAc	toluene	0
7	**L10**	NaOAc	toluene	0
8	**L11**	NaOAc	toluene	0
9	**L12**	NaOAc	toluene	0
10	**L13**	NaOAc	toluene	0
11	**L14**	NaOAc	toluene	0
12	**L15**	NaOAc	toluene	20
13	**L16**	NaOAc	toluene	40
14	**L17**	NaOAc	toluene	18
15	**L18**	NaOAc	toluene	10
16	**L19**	NaOAc	toluene	24
17	**L20**	NaOAc	toluene	35
18[b]	**L16**	NaOAc	toluene	93
19[b]	**L16**	NaOAc	THF	25
20[b]	**L16**	NaOAc	1,4-dioxane	34
21[b]	**L16**	NaOAc	DMF	52
22[b]	**L16**	NaOAc	cyclohexane	0
23[b]	**L16**	NaOAc	$CF_3C_6H_5$	95
24[b]	**L16**	NaOtBu	$CF_3C_6H_5$	8
25[b]	**L16**	Cs_2CO_3	$CF_3C_6H_5$	15
26[b]	**L16**	K_2CO_3	$CF_3C_6H_5$	46
27[b]	**L16**	KOAc	$CF_3C_6H_5$	65
28[b]	**L16**	LiOAc	$CF_3C_6H_5$	10
29[b]	**L16**	Et_3N	$CF_3C_6H_5$	12
30[c]	**L16**	NaOAc	$CF_3C_6H_5$	78
31[d]	**L16**	NaOAc	$CF_3C_6H_5$	87



[a]Unless otherwise specified, the reactions were carried out with 3-bromopyridine (**1a**) (0.25 mmol), **2** (0.375 mmol, 1.5 equiv), $Pd_2(dba)_3$ (2 mol %), **L** (4.8 mol %), base (0.5 mmol, 2.0 equiv), and ZnF_2 (0.05 mmol, 0.2 equiv) in solvent at 80 °C for 48 h. Yields were determined by ^{1}H NMR, and dimethyl fumarate was selected as internal standard. [b]**2** (0.75 mmol, 3.0 equiv), 90 °C. [c]**2** (0.75 mmol, 3.0 equiv), 90 °C and without ZnF_2. [d]**2** (0.75 mmol, 3.0 equiv), $Zn(OAc)_2$ (0.05 mmol, 0.2 equiv) at 90 °C.

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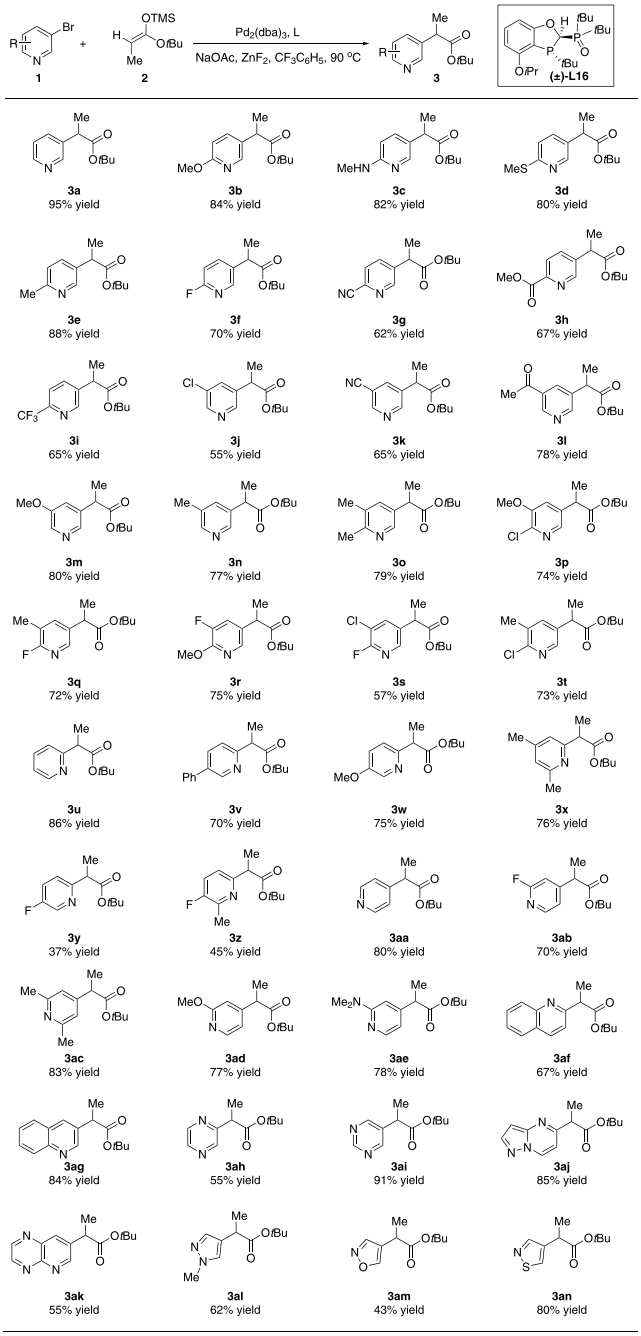
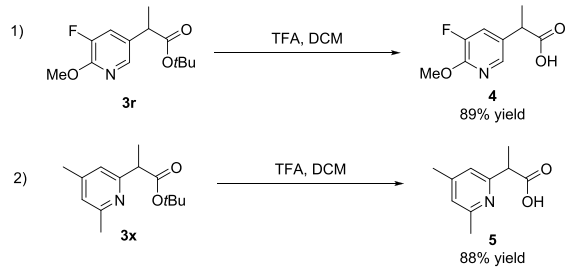
Scheme 3. Palladium-Catalyzed α-Heteroarylation between Heteroaryl Bromides 1 with (*E*)-*O*-TMS Ketene Acetal (2)[a]



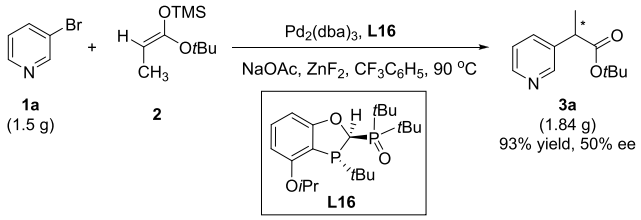
[a]Unless otherwise specified, the reactions were carried out with heteroaryl bromides **1** (0.25 mmol), **2** (0.75 mmol, 3.0 equiv), $Pd_2(dba)_3$ (2 mol %), **L16** (4.8 mol %), NaOAc (0.5 mmol, 2.0 equiv), and ZnF_2 (0.05 mmol, 0.2 equiv) in $CF_3C_6H_5$ at 90 °C for 48 h. Isolated yield.

1−10). These futile results demonstrated the challenge in accomplishing the palladium-catalyzed α-heteroarylation. When a P,P═O ligand **L15** was employed, we were pleased that the desired product **3a** was isolated in 20% yield (entry 12). Despite the less than satisfactory yield, the proof-of-concept result encouraged us to further investigate the structural effect of the P,P═O ligand on α-heteroarylation. To find a more effective ligand, a series of P,P═O ligands were synthesized[7] and screened. Ligand **L16** bearing an isopropoxy

Scheme 4. Synthetic Applications



Scheme 5. Gram-Scale Asymmetric Pd-Catalyzed Cross-Coupling between 1a and 2



group provided **3a** in 40% yield (entry 13). Surprisingly, ligands **L17** and **L19**, bearing a *tert*-butyl group and an isopentyl group, respectively, led to inferior yields (entries 14 and 16). Employment of ligand **L18** containing a $P(O)Ad_2$ group only led to 10% yield (entry 15). To our delight, employment of 3 equiv of **2** at 90 °C provided an excellent yield (entry 18). Screening of various solvents and bases showed that the use of $CF_3C_6H_5$ as the solvent and NaOAc as the base provided a better yield (entries 19−29). The addition of ZnF_2 likely serves as a Lewis acid to help activate the TMS enol ether **2** during the reaction (entry 30).[4a] A slightly diminished yield was obtained when ZnF_2 was replaced by $Zn(OAc)_2$ (entry 31).

Under the optimized reaction conditions with P,P═O ligand **L16**, *tert*-butyl-substituted (*E*)-*O*-TMS ketene acetal (**2**) was subjected to the coupling with a series of heteroaryl bromides **1** with different electronic properties and functionalities, as shown in Scheme 3. Electron-rich 3-bromopyridines with substituents at the *ortho* position provided the coupling products **3b−e** in good yields (80−88%). Likewise, products **3f−i** with electron-withdrawing substituents (2-F, 2-CN, 2-COOEt, 2-CF_3) were also formed, albeit in slightly diminished yields (65−70%). This could be due to slower transmetalation rates with electron-deficient bromopyridines, leading to formation of desbromo side products. *Meta*-substituted pyridines with either an electron-donating or -withdrawing group were also compatible under the reaction conditions and proceeded smoothly to form the corresponding products **3j−3n** in moderate to good yields. A series of *ortho*,*meta*-disubstituted pyridines bearing methyl and halogen functionalities were also applicable, providing coupling products **3o−t** in good yields. We next explored the substrate scope of 2-bromopyridines containing various functional groups (**3u−3z**). A series of 2-bromopyridines with electron-neutral or -donating substituents at the *ortho*, *meta*-, or *para*-position afforded the products (**3v**, **3w**, and **3x**) in good yields, while substrates with electron-withdrawing substituents delivered inferior yields (**3y**: 37% and **3z**: 45%). In addition, the substrate scope of 4-bromopyridines containing various functional groups was explored. It should be noted that

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various 4-bromopyridines regardless of their electronic properties and substitution patterns were suitable substrates, leading to α-arylation products such as **3ab**, **3ac**, and **3ae** in good yields. Pleasingly, heteroaryl products with multiple heteroatoms on the ring such as pyrazine (**3ah**, **3ak**), pyrimidine (**3ai**, **3aj**), pyrazole (**3al**), isoxazole (**3am**), and isothiazole (**3an**) were all formed in moderate to high yields (43−91%).

To demonstrate the synthetic practicality of this method, the preparation of several α-heteroaryl propionic acids was studied. A derivative of NSAID-type drugs, e.g., compound **4**, was prepared from *tert*-butyl ester **3r** in 89% yield by treatment with TFA.[9] Likewise, compound **5** was obtained from **3x** in 88% yield under similar reaction conditions (Scheme 4).

To explore an enantioselective version of this transformation (Scheme 5), a chiral P,P═O ligand **L16** was subjected to a gram-scale reaction between 3-bromopyridine (**1a**) and silyl ketene acetal (**2**). The desired product was afforded in 93% yield with 50% ee. Although the enantiomeric excess was only moderate, this showcases the potential to further explore an enantioselective variant of this transformation.

In summary, we have established a practical and efficient synthesis of α-heteroaryl propionic esters by palladium-catalyzed intermolecular α-heteroarylation. A wide range of α-heteroaryl propionic esters with various electronic properties and functionalities were obtained from simple starting materials in moderate to excellent yields. This work further demonstrates that the employment of the bulky P,P═O ligand can provide exceptional ability in tolerating heterocycles. The facile access to a wide range of structurally diverse α-heteroaryl propionic esters which are difficult to prepare otherwise should promote their applications in drug discovery and biomedical research.

■ ASSOCIATED CONTENT

Supporting Information

. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02257.

Experimental procedures; NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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