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Communication

C–H Activation

SPECIAL ISSUE

Ligand-Enabled γ-C(sp³)–H Acetoxylation of Triflyl-Protected Amines

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Abstract: A palladium-catalyzed γ-C(sp³)–H acetoxylation of triflyl-protected amines has been achieved. The use of pyridine or 2-alkoxyquinoline-type ligands is key to the success of this transformation. The reaction is highly diastereoselective and easily scalable, and constitutes a direct approach for the synthesis of γ-hydroxy-α-amino acids and β,γ-dihydroxy amines, which are not readily accessible by other routes.

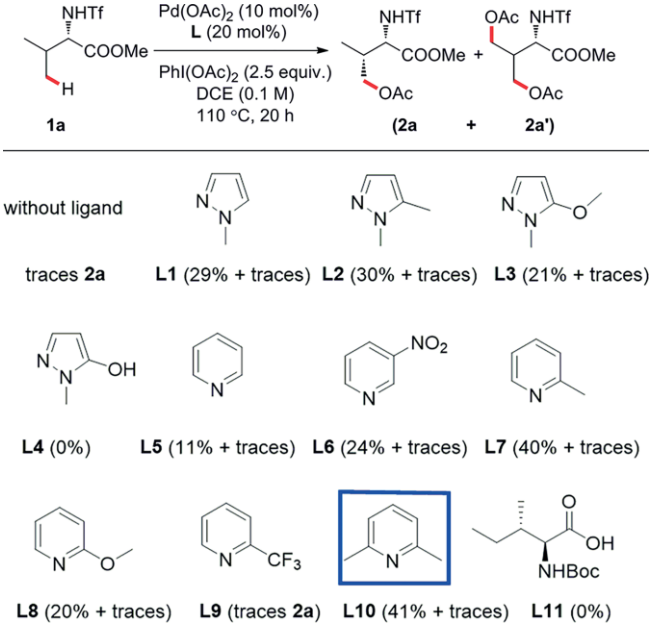
Introduction

In the past decades, palladium-catalyzed C–H functionalization reactions have attracted substantial attention from organic chemists.[1] The ability to install functionalities into molecules directly from inert C–H bonds can streamline and shorten substantially the synthesis of target compounds. A common practice to increase both the reactivity and selectivity of these processes is the use of directing groups.[2] In the case of less reactive C(sp³)–H bonds, generally, a bidentate directing group is needed in order to achieve good reactivity.[3] Recently, the direct and selective functionalization of C(sp³)–H bonds has been achieved combining monodentate directing groups and ligands.[4–6] In these transformations, the selectivity is controlled by the directing group and the ligand plays a pivotal role in increasing the reactivity of the inert C(sp³)–H bond. For example, triflyl- or nosyl-protected amines can be efficiently γ-arylated or -alkylated in the presence of mono-protected-amino acid or -aminomethyl oxazoline ligands.[4] Since amines are ubiquitous subunits in organic molecules, the development of new methodologies that permit their direct functionalization are of great interest.[7] For instance, γ-hydroxy-α-amino acids widely exist in many peptide-based drugs and can be used for native chemical ligation (NCL).[8] Although several examples of direct γ-C(sp³)–H acetoxylation of α-amino acids have been reported, they all rely on the use of a bidentate directing group to achieve good reactivity.[9] In our group, we are interested in the development of new ligands capable of promoting C–H functionalization reactions.[10] Herein, we report the first example of Pd-catalyzed γ-C(sp³)–H acetoxylation of triflyl-protected amines assisted by pyridine-based ligands.[11]

Results and Discussion

We started our investigations using methyl *N*-triflyl-L-valinate (**1a**) as the model substrate, $Pd(OAc)_2$ (10 mol-%) as the palladium catalyst and $PhI(OAc)_2$ as the oxidant, in 1,2-dichloroethane (0.1 M) at 110 °C. Under these conditions, only trace amount of acetoxylated product **2a** were detected after 20 h (Table 1).

Table 1. Screening of ligands for the γ-C(sp³)–H acetoxylation of *N*-triflyl-L-valinate.[a,b]



[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.01 mmol, 10 mol-%), ligand (0.02 mmol, 20 mol-%), $PhI(OAc)_2$ (0.25 mmol, 2.5 equiv.), DCE (1.0 mL), 110 °C, 20 h. [b] Yields were determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

In order to increase the reactivity of the C(sp³)–H bond, we decided to evaluate different ligands in this transformation. Thus, under the standard reaction conditions, the addition of 1-methylpyrazole (**L1**, 20 mol-%) provided the desired acetoxylated product **2a** in 29 % yield, together with trace amount of diacetoxylated product **2a′**. Encouraged by this result, other protected 1-methylpyrazole-type ligands were tested. The 5-methyl-substituted ligand **L2**, exhibited similar behaviour (30 % yield) than **L1**. When the 5-position of the pyrazole ligand

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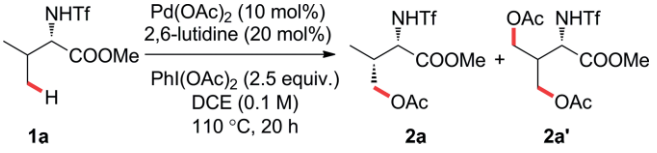
beared a methoxy group, only 21 % yield of the desired product was detected, while the unprotected 5-hydroxy-1-methylpyrazole (**L4**) completely inhibited the reaction. Pyridine-type ligands are known to be effective ligands in C–H functionalization reactions.[12] Therefore, we evaluated their effect in the C(sp^3)–H acetoxylation reaction. The model reaction in the presence of pyridine (**L5**) furnished **2a** in 11 % yield. The electron-deficient 3-nitropyridine ligand (**L6**) provided improved results compared with pyridine, giving **2a** in 24 % yield. We also tested different 2-substituted pyridine ligands. The use of 2-picoline (**L7**) improved the yield of **2a** up to 40 %. The introduction of a methoxy group in the pyridine ring (**L8**) showed once more negative effects in the reaction (20 % yield). Very low conversion was also observed when 2-(trifluoromethyl)pyridine (**L9**) was employed as ligand, but the reaction in the presence of 2,6-lutidine (**L10**) gave **2a** in 41 % yield. It is worth mentioning that the reaction proceeds cleanly and mainly the acetoxylated product and starting material were detected in the crude mixture. Finally, we also tried the reaction using a mono-protected amino acid ligand, Boc-L-isoleucine (**L11**), which was an efficient ligand in the C(sp^3)–H γ-arylation and -alkylation of triflyl- or nosyl-protected amines.[4a,4b] However, under our reaction conditions, no acetoxylated product was detected.

With a suitable ligand in hand, other reaction conditions were evaluated (Table 2). A systematic screening of solvents revealed that dichloromethane (DCM) gave similar yield (42 %) than 1,2-dichloroethane (entries 1–2). Other solvents such as toluene or acetonitrile provided the monoacetoxylated product **2a** in lower yields (26 % and 21 % yield, respectively; entries 3–4). When using AcOH as solvent, almost no conversion was obtained (entry 5). When the reaction was performed at higher concentration (0.5 M DCM) similar yield for **2a** was obtained (entry 6). Having identified the best solvent, we tested other co-oxidants in the reaction. Although the use of $PhCO_3tBu$ completely inhibited the reaction (entry 7), the conversion was improved to 63 % and 59 % when AgOAc and $K_2S_2O_8$ were employed, respectively (entries 8–9). We further screened other pyridine and 2-alkoxyquinoline-type ligands using DCM as solvent and AgOAc as co-oxidant (see Supporting Information, Table S4). We found out that some 2-alkoxyquinoline ligands (**L21**–**L23**) provided comparable yields of acetoxylated products **2a** and **2a′** than 2,6-lutidine. Given that 2,6-lutidine is easily accessible, we used it as the optimal ligand for further screening of reaction conditions. Different palladium sources were evaluated (entries 10–13), and only $Pd(OPiv)_2$ furnished slightly better yield than $Pd(OAc)_2$. The reaction using $Pd(OPiv)_2$ and 1 equiv. of AgOAc furnished the acetoxylated products in 63 % total isolated yield (56 % monoacetoxylated product **2a** and 7 % diacetoxylated product **2a′**, entry 14). We performed a control experiment in the absence of palladium-catalyst and, as expected, no conversion to the desired product was observed (entry 15). Finally, we executed the reaction in the absence of 2,6-lutidine (**L10**) under the optimal reaction conditions and only 17 % yield was detected, which highlights the crucial role of the ligand in this transformation (entry 16). Important features of the 2,6-lutidine enabled C(sp^3)–H γ-acetoxylation of methyl *N*-triflyl-L-valinate (**1a**) are that the monoacetoxylated product was obtained with very high diastereoselectivity (*dr* = 13:1; determined by ^{1}H-NMR) and that no-gemdiacetoxylated product was observed. The synthetic utility of our methodology was highlighted in a scale-up of the reaction to a 1.0 mmol of **1a**, providing the acetoxylated products in comparable yields than to the original value (Table 3).

Table 2. Optimization of reaction conditions.



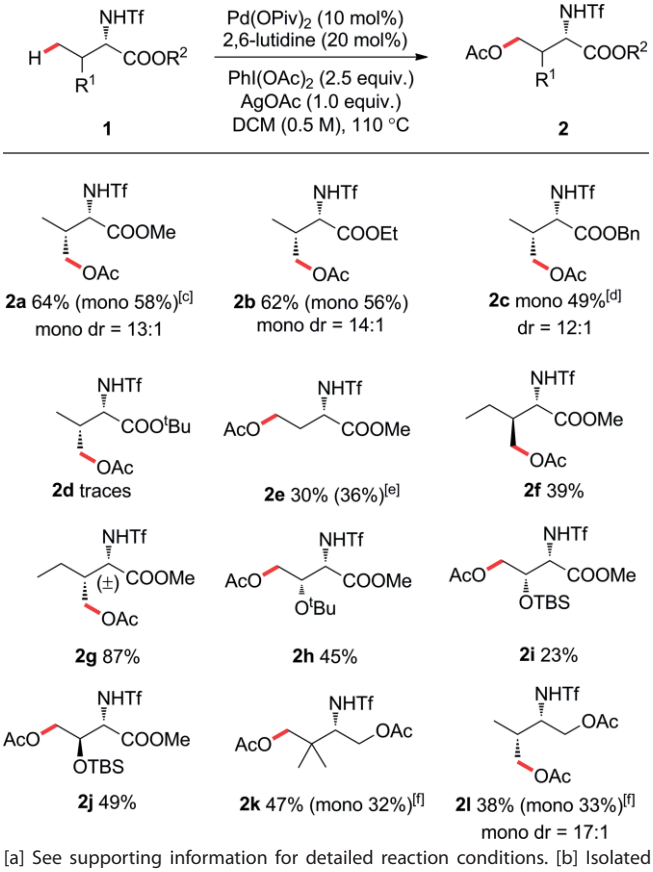
1a **2a** **2a'**

Entry	Variations from standard reaction conditions	Yield[a] (**2a** + **2a′**)
1	None	41 % + traces
2	DCM as solvent	42 % + traces
3	Toluene as solvent	26 % + traces
4	CH_3CN as solvent	21 % + traces
5	AcOH/Ac_2O (9:1, v/v) as solvent	< 10 %
6	DCM (0.5 M)	42 % + 3 %
7	$PhCO_3tBu$ (2.0 equiv.), DCM (0.5 M)	traces
8	AgOAc (2.0 equiv.), DCM (0.5 M)	58 % + 5 %
9	$K_2S_2O_8$ (2.0 equiv.), DCM (0.5 M)	53 % + 6 %
10	$PdCl_2$, AgOAc (2.0 equiv.), DCM (0.5 M)	32 % + 2 %
11	Na_2PdCl_4, AgOAc (2.0 equiv.), DCM (0.5 M)	25 % + traces
12	$Pd(TFA)_2$, AgOAc (2.0 equiv.), DCM (0.5 M)	41 % + 2 %
13	$Pd(OPiv)_2$, AgOAc (2.0 equiv.), DCM (0.5 M)	62 % + 7 %
14	$Pd(OPiv)_2$, AgOAc (1.0 equiv.), DCM (0.5 M)	60 % + 7 %, (56 % + 7 %)[b]
15	No Pd-catalyst, AgOAc (1.0 equiv.), DCM (0.5 M)	0 %
16	No ligand, AgOAc (1.0 equiv.), DCM (0.5 M)	17 % + traces

[a] The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. [b] Isolated yield.

With the optimized reaction conditions in hand, we sought to explore the substrate scope and limitations of this transformation (Table 3). First, we tested different alkyl *N*-triflyl amino esters. The reaction with ethyl (**1b**) or benzyl (**1c**) *N*-triflyl-L-valinate provided the desired monoacetoxylated product in 56 % and 49 % yield, respectively, with very high diastereoselectivity. However, only trace amount of product was detected when *tert*-butyl *N*-triflyl-L-valinate (**1d**) was used. The reaction with the more conformationally flexible methyl *N*-triflyl-L-homoalaninate (**1e**) provided the corresponding γ-acetoxylated product in moderate yield (36 %). The reaction with *N*-triflyl isoleucine and alloisoleucine derivatives showed a very different reactivity profile in agreement with the high stereoselectivity observed in the reaction with *N*-triflyl-L-valinates. While the reaction with the isoleucine derivative **1f** provided the acetoxylated product **2f** in 39 % isolated yield, the diastereoisomeric alloisoleuceine derivative **1g** furnished the acetoxylated product **2g** in 87 % isolated yield. The difference in reactivity between the two diastereoisomers can be attributed to the greater accessibility of the C(sp^3)–H bond in the palladation step. Indeed, this behaviour has been previously observed in other C(sp^3)–H functionalization reactions of amino acid derivatives.[3e,3h] Taking into consideration the outcome of the reaction of *N*-triflyl isoleucine **1f** and alloisoleucine **1g**, we propose that the γ-acetoxylation of valine derivatives **1a**–**c** occurs mainly at the pro-*R* methyl group.

Table 3. Substrate scope.[a,b]



[a] See supporting information for detailed reaction conditions. [b] Isolated yields. [c] The reaction was performed on a 1.0 mmol scale. [d] From ^{1}H NMR analysis of the crude mixture, the conversion to diacetoxylated product was *ca* 5 %. The diacetoxylated product could not be isolated pure by column chromatography. [e] 20 mol-% of $Pd(OPiv)_2$ and 40 mol-% of ligand were used. [f] **L22** was used instead of 2,6-lutidine.

The reaction with the *O*-*t*Bu threonine derivative **1h**, under optimized reaction conditions, provided the γ-acetoxylated product **2h** in 45 % isolated yield. When the reaction was performed with the *O*-TBS protected threonine derivative **1i** the product **2i** was obtained in lower yield (23 %). Nevertheless, when the reaction was carried out with *O*-TBS allothreonine derivative **1j**, the acetoxylated product was formed in higher yield (49 %). Finally, we evaluated if amino alcohols were suitable substrates for this transformation. When we performed the reaction of *O*-acetyl-*N*-triflyl-L-*tert*-leucinol (**1k**) under the optimized reaction conditions, only 20 % ^{1}H-NMR yield was obtained. Fortunately, the use of the 2-alkoxyquinoline ligand **L22**, which had proved equally efficient than 2,6-lutidine in the C–H acetoxylation of amino acid derivatives (see supporting information, Table S10), provided the acetoxylated products in 47 % isolated yield. Similarly, the reaction of *O*-acetyl-*N*-triflyl-L-valinol (**1l**), using **L22** as external ligand, provided 38 % total yield of acetoxylated products, being the monoacetoxylated product **2l** obtained with high diastereoselectivity (*dr* = 17:1; determined by ^{1}H-NMR).[13]

On the basis of previous reports, a plausible mechanism for this transformation is presented in Figure 1.[4c,14] First, we postulate that the palladium(II) coordinates to the nitrogen followed by the γ-C(sp^3)–H activation and oxidative addition of $PhI(OAc)_2$ to form organopalladium(IV) complex. This palladium(IV) complex can then undergo a C–O bond reductive elimination to form the acetoxylated product and the palladium(II) catalyst.

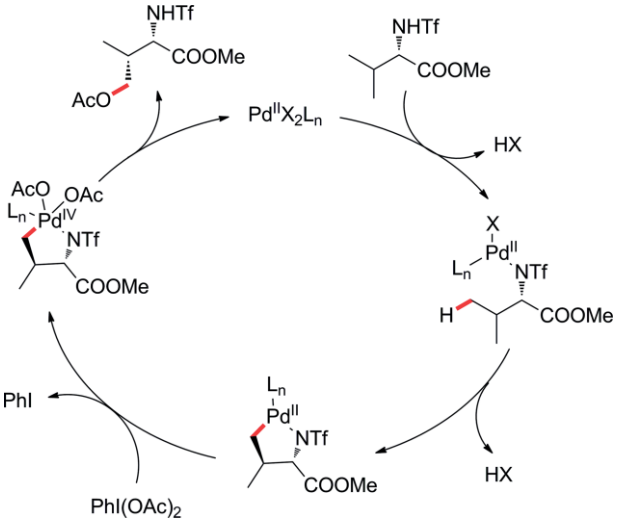


Figure 1. Proposed catalytic cycle.

Conclusions

In summary, we have developed a palladium-catalyzed γ-C(sp^3)–H acetoxylation of *N*-trifyl protected amines. The key to the success of this transformation is the use of pyridine or 2-alkoxyquinoline-type ligands. The reaction is highly diastereoselective and takes place with a variety of amino acid and amino alcohol derivatives in moderate to good yields. This protocol is easily scalable and constitutes a direct approach for the synthesis of γ-hydroxy-α-amino acids and β,γ-dihydroxy amines, which are not readily accessible by other routes. Future efforts will focus on improving the efficiency of these transformations by ligand design.

Acknowledgments

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Keywords: C–H activation · Amines · Ligand design · Palladium · Acetoxylation

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