Tetrahedron Letters 53 (2012) 6853–6857

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of γ-fluoroalkylated allylic amine derivatives via palladium-catalyzed Overman rearrangement

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ARTICLE INFO

Article history:
Received 14 August 2012
Revised 25 September 2012
Accepted 9 October 2012
Available online 16 October 2012

Keywords:
γ-Fluoroalkylated allylic amines
Palladium-catalyzed
Overman rearrangement

ABSTRACT

A Pd-catalyzed Overman rearrangement of α-fluoroalkylated allylic trichloroacetimidates has been developed. This reaction allows for an efficient synthesis of γ-fluoroalkylated allylic amine derivatives with excellent regio- and stereo-selectivities under mild conditions.

Overman rearrangement is a pivotal method for the construction of relatively inaccessible allylic amine derivatives from readily available allylic alcohols.[1–3] This transformation can be achieved by elevated temperature or by transition-metal catalysis under mild conditions.[1,2] Since the first report in 1974,[1a] Overman rearrangement has found widespread application in organic synthesis. However, only scattered examples for the Overman rearrangement of fluorinated allylic alcohol derivatives to fluorinated allylic amine derivatives have been reported.[3] Fluorinated allylic amines are versatile synthetic intermediates for the preparation of a series of structurally complicated fluorinated molecules.[3–5] Among them, γ-fluoroalkylated allylic amines **1** are of particular interest to synthetic chemists, because γ-fluoroalkylated allylic amines not only can be found in biological active agents such as the bioprotective agent JP4-039 analogues but also are the most important precursors to biologically important compounds such as β-glucosidase selective inhibitors *gem*-difluoromethylenated azasugars.[4,5] However, strategies for the preparation of γ-fluoroalkylated allylic amines have been less exploited, especially for the preparation of optically active γ-fluoroalkylated allylic amines. Generally, these compounds can be prepared by Pd-catalyzed allylic amination (Scheme 1a).[5] Despite the utility of these methods, the requirement of harsh conditions for the removal of N-protecting groups restricted their widespread synthetic applications. Thus, the development of more general and efficient method for the preparation of γ-fluoroalkylated allylic amines is still highly desirable. Herein, we describe the first example of Pd-catalyzed Overman rearrangement of α-fluoroalkylated allylic trichloroacetimidates (Scheme 1b). This transformation provides a highly regio- and stereo-selective method for the preparation of γ-fluoroalkylated allylic amines with high operational simplicity and easy removal of N-protecting group (see Fig. 1).

Initially, we probe the optimal reaction conditions using α-difluoromethylated allylic trichloroacetimidate **2a** as the model substrate. However, none of the desired γ-difluoromethylated allylic trichloroacetamide **3a** was observed using either CH_2Cl_2 or toluene as a solvent at reflux under traditional thermal rearrangement reactions (Table 1, entries 1–2). K_2CO_3, which is commonly used to facilitate the Overman rearrangement under the thermal conditions,[6] proved to be completely ineffective in the current reaction (entry 3). The further investigation focused on identifying a palladium catalyst capable of catalyzing the desired rearrangement reaction of **2a** under mild conditions. Indeed, when **2a** was treated with 5 mol % $[PdCl_2(MeCN)_2]$ in CH_2Cl_2 at reflux for 4 h, the rearranged product **3a** was obtained in 95% yield (entry 4). The screening of Pd(II) catalysts showed that only $[PdCl_2(MeCN)_2]$ was reactive, whereas other Pd(II) species such as $[PdCl_2(PPh_3)_2]$, $Pd(OAc)_2$, and $PdCl_2$ were ineffective in the current reaction

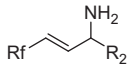

Figure 1. γ-Fluoroalkylated allylic amines **1**.

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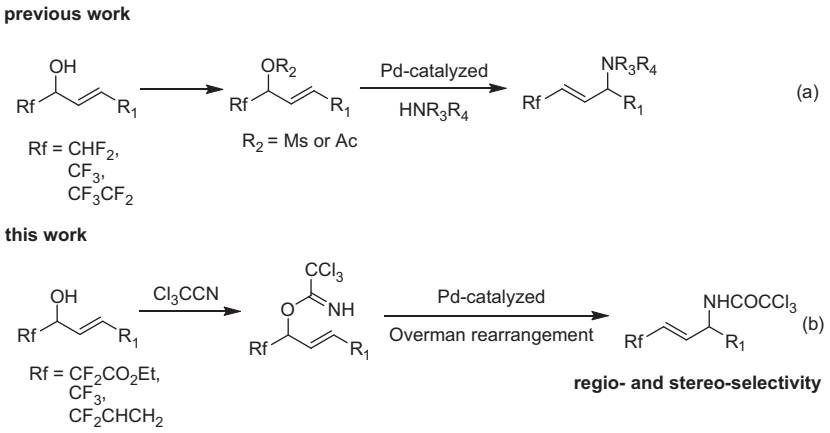
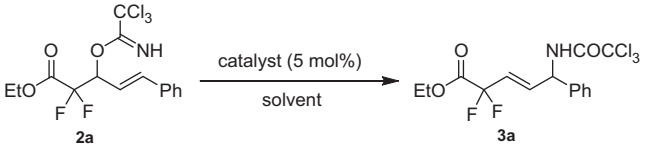
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.045



Scheme 1. Synthetic methods for γ-fluoroalkylated allylic amines.

Table 1
Optimization of Overman rearrangement of **2a**[a]



2a **3a**

Entry	Solvent	Additive	Catalyst (mol %)	Yield[b] of **2a** (%)
1	CH_2Cl_2	—	—	0
2[c]	Toluene	—	—	0
3[c]	Toluene	K_2CO_3	—	0
4	CH_2Cl_2	—	$PdCl_2(MeCN)_2$ (5.0)	95
5	CH_2Cl_2	—	$PdCl_2(PPh_3)_2$ (5.0)	0
6	CH_2Cl_2	—	$Pd(OAc)_2$ (5.0)	0
7	CH_2Cl_2	—	$PdCl_2$ (5.0)	0
8[d]	CH_2Cl_2	—	$PdCl_2(MeCN)_2$ (5.0)	0
9[e]	CH_2Cl_2	—	$PdCl_2(MeCN)_2$ (1.5)	31

[a] Reaction conditions: **2a** (0.2 mmol), additive (0.2 mmol), catalyst (5 mol %), solvent (4 mL), N_2, 4 h, reflux.
[b] Yields of **3a** were determined by ^{19}F NMR with benzotrifluoride as an internal standard.
[c] Reaction was conducted at 110 °C.
[d] Reaction was conducted at room temperature.
[e] In the presence of 1.5 mol % of $PdCl_2(MeCN)_2$.

(entries 4–7). Control experiments revealed that reaction temperature is critical to this transformation. Starting material **2a** remained intact when the transformation was carried out at room temperature in CH_2Cl_2 (entry 8). The Pd-catalyzed Overman rearrangement reaction could be performed in the presence of 1.5 mol % of [$PdCl_2(MeCN)_2$], albeit with a bit lower yield (entry 9).

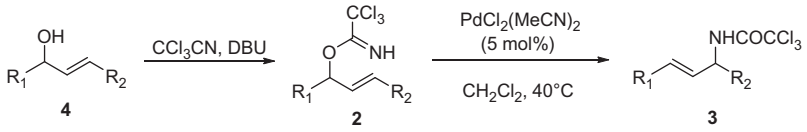
With the optimized reaction conditions in hand, we next examined the substrate scope of the Pd-catalyzed Overman rearrangement reactions of α-fluoroalkylated allylic alcohol derivatives. As shown in Table 2, the electron-rich and electron-deficient aryl group at the C1 position of α-difluoromethylated allylic trichloroacetimidates (**2a–d**) underwent the desired rearrangement, affording the corresponding (*E*)-difluoromethylated allylic trichloroacetamides (**3a–3d**) in high yields (Table 2, entries 1–4). These results showed that the electronic nature of the substituents on the aryl rings has no significant effect on the efficiency. Notably, the substrate **2d** bearing a terminal alkene group at the C3 position was tolerated and furnished the corresponding product **3d** in an excellent yield (entry 4). The C1-alkyl substituted substrates (**2e–g**) were also compatible with this catalytic transformation, and all reactions produced the desired products (**3e–g**) in good yields (entries 5–7). However, the reaction of substrate **2h** was ineffective under the standard condition, and the modification of catalyst loading (30 mol %) and reaction temperature (reflux in toluene) was needed to achieve a moderate yield of **3h** (entry 8). Furthermore, a series of allylic trichloroacetimidates containing the CF_3 group at the C3 position rearranged cleanly to provide the corresponding products in high to excellent yields (entries 9–15). This method tolerates many common functionalities including alkene and silyl ether, which is very attractive for the preparation of synthetically useful γ-fluoroalkylated allylic amines (entries 4, 7, 14–15). Importantly, the rearrangement of chiral (*R*)-allylic trichloroacetimidate **2d**, which was prepared from racemic allylic alcohol **4d** via a multi-step synthesis,[7] proceeded readily to deliver the desired product (*S*)-**3d** with no detectable loss of enantiomeric purity (Scheme 2). This result also indicated that the current Pd-catalyzed Overman rearrangement of α-fluoroalkylated allylic trichloroacetimidates occured via the generally accepted pathway.[2,8] Furthermore, removal of the trichloroacetyl group from (*S*)-**3d** was achieved by treatment with KOH under EtOH/H_2O reflux,[2k] affording α-fluoroalkylated allylic amine **6** in 56% yield (Scheme 2).

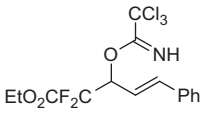
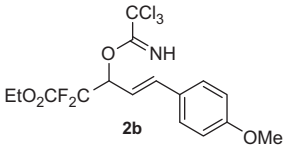
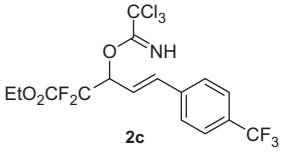
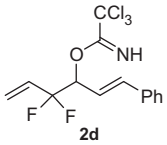
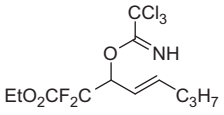
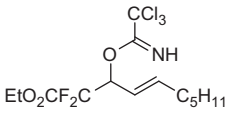
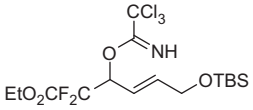
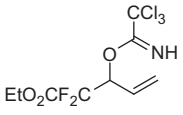
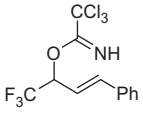
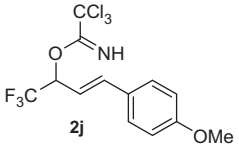
In conclusion, a Pd-catalyzed Overman rearrangement of α-fluoroalkylated allylic trichloroacetimidates has been developed, providing a series of γ-fluoroalkylated allylic amine derivatives in moderate to excellent yields. Because of the high potential utility of fluoroalkylated allylic amines, the excellent regioselectivity and stereoselectivity, good functional group compatibility, and mild reaction conditions, we expect this method would find wide applications in pharmaceutical and agrochemical fields.

Acknowledgments

We thank the National Natural Science Foundation of China (21072018, 20632008, and 21272036) and the National Basic Research Program of China (973 Program, No. 2012CB821600) for funding this work.

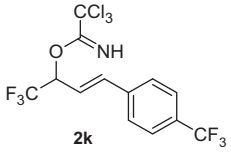
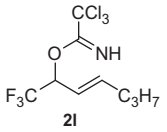
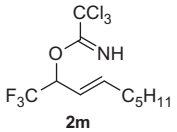
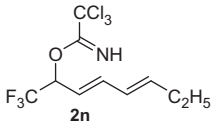
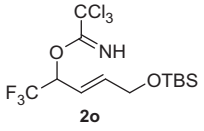
Table 2
Substrate scope of Pd-catalyzed Overman rearrangement of fluoroalkylated allylic trichloroacetimidates **2**[a]



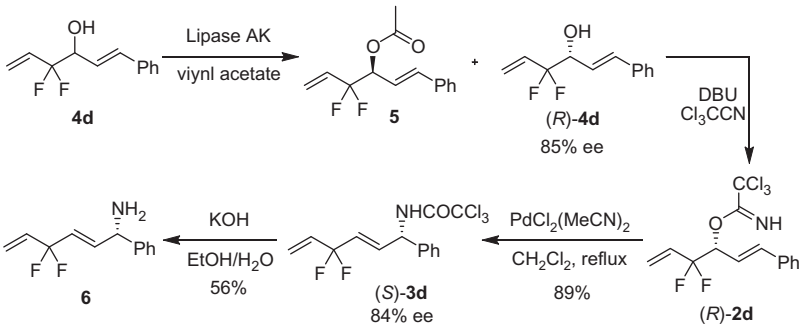
Entry	Substrate **2**	Product **3**	Yield[b,c] (%)
1	 **2a**	**3a**	87
2	 **2b**	**3b**	83
3	 **2c**	**3c**	84
4	 **2d**	**3d**	92
5	 **2e**	**3e**	79
6	 **2f**	**3f**	75
7	 **2g**	**3g**	85
8[d]	 **2h**	**3h**	60
9	 **2i**	**3i**	90
10	 **2j**	**3j**	87

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate **2**	Product **3**	Yield[b,c] (%)
11	 **2k**	**3k**	85
12	 **2l**	**3l**	91
13	 **2m**	**3m**	92
14	 **2n**	**3n**	78
15	 **2o**	**3o**	93

[a] All reactions were performed by using 5 mol % $PdCl_2(MeCN)_2$ in CH_2Cl_2 at reflux, unless otherwise noted.
[b] Isolated yields in two steps from alcohol **4**.
[c] *E*-Isomers were produced exclusively in all cases.
[d] The reaction was carried out in toluene at reflux in the presence of 30 mol % of $PdCl_2(MeCN)_2$.



Scheme 2. Overman rearrangement of (*R*)-**2d**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.045.

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8. Determination of the absolute stereochemistry of chiral product **3d** derived from precursor **2d** on the basis of the tight six-membered chair-like transition state (Ref. 2).