Tetrahedron Letters 58 (2017) 2525–2529

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Direct palladium-catalyzed allylic alkylations of alcohols with enamines: Synthesis of homoallyl ketones

Ghalia Bouhalleb [a], Olfa Mhasni [b], Giovanni Poli [c], Farhat Rezgui [a,*]

[a] Université de Tunis EL Manar, Faculté des Sciences, Laboratoire de Chimie Organique Structurale Campus Universitaire, 2092 Tunis, Tunisia
[b] Institute for Research and Physicochemical Analysis (INRAP), Pôle Technologique, Sidi Thabet, Tunisia
[c] Institut Parisien de Chimie Moléculaire (IPCM), UMR 8232 Sorbonne Universités, UPMC Univ Paris 06, CNRS 4 place Jussieu, 75005 Paris, France

ARTICLE INFO

Article history:
Received 21 February 2017
Revised 29 April 2017
Accepted 9 May 2017
Available online 11 May 2017

Keywords:
Allylic substitution
Homoallyl ketone
Enamine
Palladium
Allylic alcohol

ABSTRACT

An efficient, direct nucleophilic allylic substitution of α-, β- and γ-substituted alcohols with enamines, using the $Pd(OAc)_2/PPh_3$ catalyst system and $ZnBr_2$ as a promoter in CH_2Cl_2 at reflux, is reported. The reaction course was dependent on the steric hindrance at the α- or γ-positions with respect to the functionalized α-carbon, selectively affording in moderate to good yields, α- or γ-homoallyl ketones, the so-called "linear" and "branched" products, respectively.

Introduction

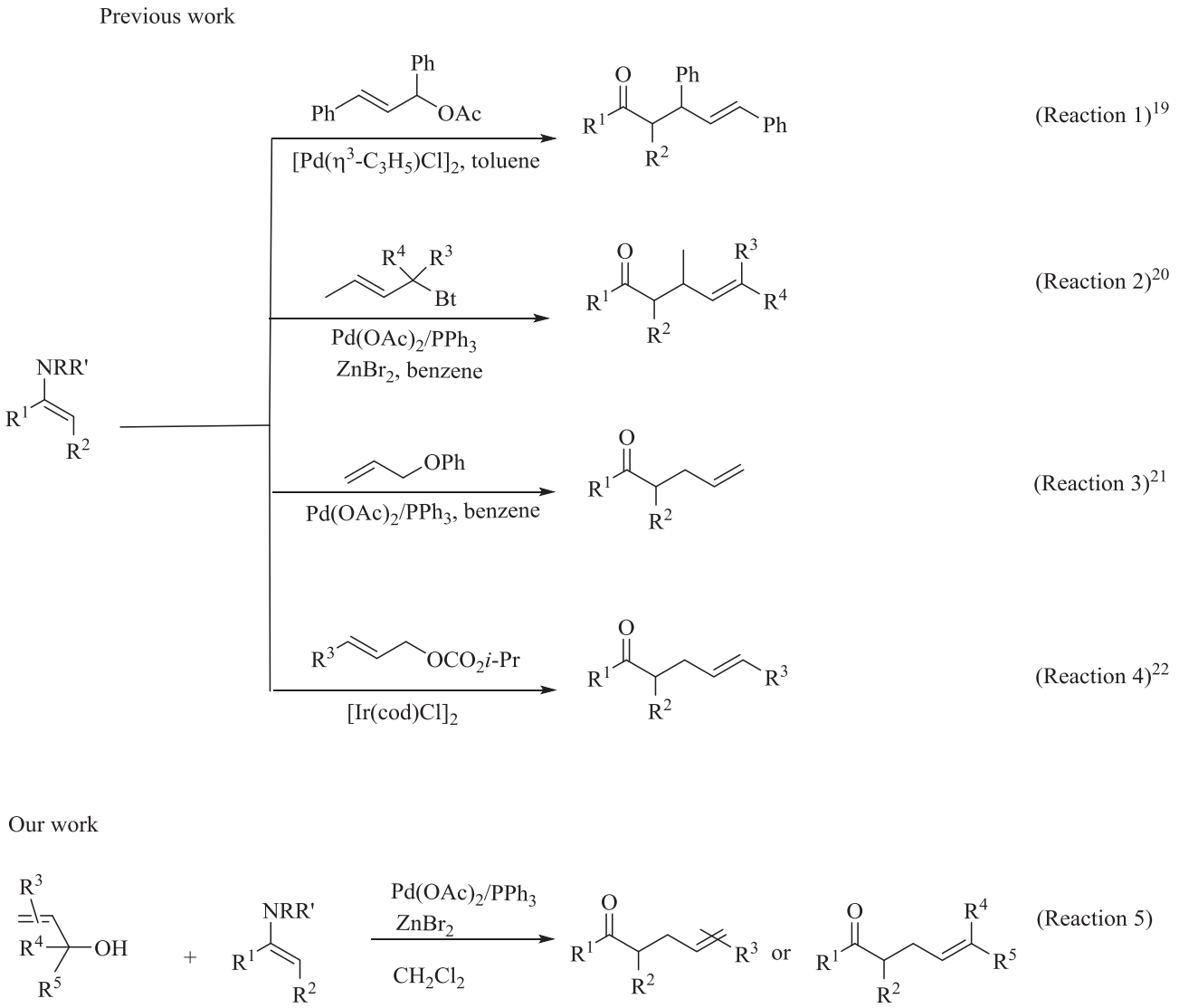
Homoallyl ketones are organic compounds possessing a γ,δ-enone system which are useful intermediates for the synthesis of various compounds, including 1,2,4-trioxanes such as artemisinin,[1] and six-membered cyclic peroxides, some of which exhibit antifungal activities.[2] The intramolecular, $EtAlCl_2$ mediated cyclization of homoallyl ketones was also implemented for construction of the hydrazulenone ring of the diterpene antibiotic guanacasterpene.[3]

The most common approach for the synthesis of homoallyl ketones is the conjugate addition of alkenyl carbanions onto Michael acceptors, e.g. 1,4-addition of lithium alkenyl cuprates,[4] 1-alkenyldialkoxyboranes,[5] alkenylboronic acids,[6] 2-benzotriazolylethylsilanes,[7] or α-zirconated vinyl silanes[8] onto α,β-unsaturated ketones. Furthermore, the addition of alkenyl Grignard-copper(I) reagents onto carboxylic esters,[9] the thermal Claisen rearrangement of allyl vinyl ethers,[10] and the photocatalytic Norrish type I reaction of cyclopentanones[11] were also reported to afford homoallyl ketones. The synthesis of homoallyl ketones can also be achieved through the allylic alkylation of ketones with allylic compounds, e.g. alcohols,[12] acetates[13] and amines,[14] using a combination of palladium and organic catalysis involving, for instance, *in situ* generated enamines. Additionally, homoallyl ketones were prepared by the allylic alkylation of ketones, as well as silyl enol ethers or enamines as their synthetic equivalents, in the presence of Lewis or Brønsted acids and transition-metals. In this context, Saigo and co-workers reported the regioselective reaction of allylic acetates with silyl enol ethers in the presence of catalytic TMSOTf.[15] On the other hand, the nucleophilic behavior of enamines, as preformed reagents instead of being generated *in situ*, was explored in various transition-metal-catalyzed allylic alkylation reactions in which palladium played an important role.[16–18] Indeed, the Pd(II) catalyzed reaction of enamines with allylic compounds such as acetates[19] (Scheme 1, Reaction 1), benzotriazoles[20] (Reaction 2), and phenyl ethers[21] (Reaction 3) works well. More recently, iridium was also reported to efficiently catalyze the allylation of enamines with allyl carbonates (Reaction 4).[22]

It is notable that the direct use of allylic alcohols, instead of the corresponding activated substrates possessing good leaving groups (LG = OAc, OCO_2R), remains a challenge in palladium-catalyzed allylic substitutions.[23] To the best of our knowledge, the allylic alkylation of preformed enamines with allylic alcohols in the presence of palladium as a catalyst or Lewis acids as promotors, has not been previously reported. Therefore, in continuation of our interest in direct allylic substitution reactions with unactivated allylic substrates,[24] we herein report a synthetic approach towards homoallyl ketones *via* the reaction of allylic alcohols with enamines in the presence the $Pd(OAc)_2/PPh_3$ system and $ZnBr_2$ which could assist the departure of the hydroxyl group (Reaction 5).[25]

* Corresponding author.
E-mail address: rez_far@yahoo.fr (F. Rezgui).

http://dx.doi.org/10.1016/j.tetlet.2017.05.024
0040-4039/



Scheme 1. Selected Pd- and Ir-catalyzed allylic alkylations of enamines.

Results and discussion

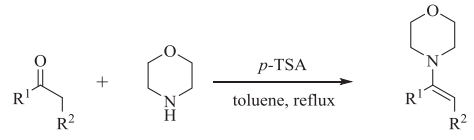
Enamines **2a–d** were prepared from the reaction of the corresponding ketones **1a–d** with morpholine (Table 1).[26]

Upon treatment of the model enamine **2b** (5 equiv.) with allylic alcohol **3a** (1 equiv.) at room temperature, then at reflux under solvent-free conditions or in CH_2Cl_2 without any additive, the starting materials were recovered after 72 h (Table 1, entries 1, 2). Therefore, we opted to continue further experiments using palladium which has been demonstrated as an efficient catalyst in nucleophilic allylic substitutions. After optimization of the reaction conditions [$Pd(OAc)_2$ (4 mol%) /PPh_3 (16 mol%), $ZnBr_2$ (2.66 equiv.)], the reaction of allyl alcohol **3a** (1 equiv.) with enamine **2b** (5 equiv.) in CH_2Cl_2 at reflux afforded homoallyl ketone **4a** in 80% yield after 2 h (Entry 3) (Table 2).[32]

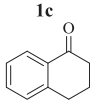
In order to investigate the reaction scope, a variety of differently α-, β- and δ-substituted primary, secondary and tertiary allylic alcohols were selected. Under the optimized conditions, treatment of the β-substituted primary alcohols **3b**,**c** with enamines **2a–c** exclusively gave homoallyl ketones **4b–f** in good yields (Table 3, entries 2–6).

It is worth noting that in the allylic alkylation of alcohols **3a–c**, the problem of regioselectivity does not arise since the resulting α- and δ-products are identical, and therefore, in each of these

Table 1
Synthesis of enamines **2a–d** from the reaction of ketones **1a–d** with morpholine.[a]



1a-d **2a-d**

Entry	Ketone	Time (h)	Yield **2** (%)
1	 **1a**	48	60
2	 **1b**	4	70
3	 **1c**	12	79
4	 **1d**	72	52[b]

[a] Reagents and conditions: ketone **1** (1 equiv.), morpholine (2 equiv.), *p*-TSA (2 equiv.), toluene, reflux (Dean-Stark apparatus).
[b] *p*-TSA (10 mol%) was used.