Tetrahedron 70 (2014) 3342–3348

Contents lists available at ScienceDirect

Tetrahedron

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

Ruthenium-catalyzed oxidative alkyne annulation by C–H activation on ketimines

Jie Li, Lutz Ackermann *

Institut fuer Organische und Biomolekulare Chemie, Georg-August Universitaet, Tammannstrasse 2, 37077 Goettingen, Germany

ARTICLE INFO

Article history:
Received 6 September 2013
Accepted 4 October 2013
Available online 10 October 2013

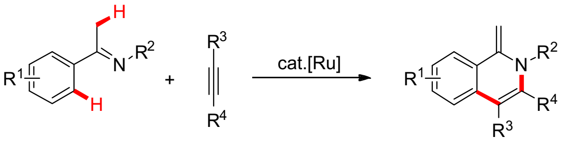
Keywords:
C–H activation
Isoquinolines
Heterocycles
Ketimines
Multicatalysis
Ruthenium

ABSTRACT

Carboxylate assistance allowed for ruthenium(II)-catalyzed oxidative alkyne annulations by ketimines under an ambient atmosphere of air. The ruthenium catalyst outperformed representative rhodium and palladium complexes, and provided versatile access to differently decorated 1-methylene-1,2-dihydroisoquinolines in a highly step- and atom-economical manner. Detailed mechanistic studies provided evidence for an initial reversible C–H bond activation event.

1. Introduction

Isoquinolines are key structural motifs of various heterocyclic[1,2] compounds with inter alia cardiovascular, anti-inflammatory or anti-malarial bioactivities.[3] As a consequence, there is a continued strong demand for methods that allow for the efficient assembly of this heterocycle. For instance, *ortho*-halo-substituted aromatic imines have been utilized for transition-metal-catalyzed annulations to furnish diversely decorated isoquinolines.[4] However, a more step-economical approach is represented by the catalyzed activation of otherwise unreactive C–H bonds, because these reactions avoid the synthesis and use of prefunctionalized starting materials.[5] Thus, in recent years we[5b,6] and others have developed ruthenium-[7] or rhodium-catalyzed[5i,8] isoquinoline syntheses exploiting C–H bond functionalizations.[6d,9] In contrast, we wish to report herein on a novel oxidative alkyne annulation that utilizes easily accessible ketimines **1**[10] and provides an expedient access to *exo*-methylene-1,2-dihydroisoquinolines **3** (Scheme 1). Notably, ruthenium catalyst proved to be optimal for this formal C–H activation process and thus outperformed representative rhodium and palladium catalysts.



1 **2** **3**

Scheme 1. Catalyzed C–H functionalization for the synthesis of dihydroisoquinolines **3**.

2. Results and discussion

2.1. Optimization studies

At the outset of our studies, we probed various reaction conditions for the desired ruthenium(II)-catalyzed oxidative C–H bond functionalization utilizing ketimine **1a**, along with $Cu(OAc)_2 \cdot H_2O$ as the oxidant (Table 1). Preliminary experiments indicated DCE to be the solvent of choice, while significantly lower yields were obtained with *t*-AmOH, MeOH, H_2O, DMF or toluene. As to cocatalytic additives, KPF_6 and KO_2CMes proved to be suitable. Yet, most effective catalysis was accomplished with $AgSbF_6$ (entries 1–4), which is likely due to the in situ formation of a cationic ruthenium catalyst. It is noteworthy that the C–H bond functionalization proceeded efficiently under an ambient atmosphere of air, thereby highlighting the user-friendly nature of our protocol (entry 5). Replacing the oxidant $Cu(OAc)_2 \cdot H_2O$ by $CuBr_2$ did shut down the

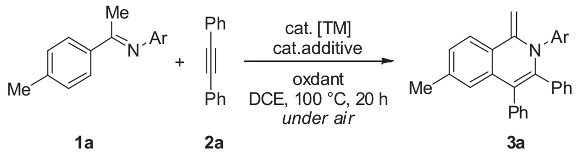
---

* Corresponding author. Tel.: +49 551 393202; fax: +49 551 396777; e-mail addresses: lutz.ackermann@chemie.uni-goettingen.de, lackerm@gwdg.de (L. Ackermann).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.10.003

oxidative alkyne annulation (entry 6). Interestingly, the catalytic activity was restored through the addition of metal acetates, indicating carboxylate assistance to be of prime importance for the C–H bond functionalization (entries 7–9).[7b] Notably, we found that the ruthenium(II) catalyst outcompeted typical rhodium or palladium complexes (entries 5, 10, and 11).

Table 1
Optimization of the oxidative annulation with ketimine **1a**[a]



Entry	Catalyst	Additive	Oxidant	3a
1	—	—	$Cu(OAc)_2 \cdot H_2O$	—
2	$[RuCl_2(p\text{-cymene})]_2$	KPF_6	$Cu(OAc)_2 \cdot H_2O$	51%[b]
3	$[RuCl_2(p\text{-cymene})]_2$	KO_2CMes	$Cu(OAc)_2 \cdot H_2O$	61%[b]
4	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	67%[b]
5	$\mathbf{[RuCl_2(p\text{-cymene})]_2}$	$\mathbf{AgSbF_6}$	$\mathbf{Cu(OAc)_2 \cdot H_2O}$	**71%**
6	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	$CuBr_2$	—
7	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	$CuBr_2/NaOAc$[c]	54%
8	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	$CuBr_2/KOAc$[c]	53%
9	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	$CuBr_2/CsOAc$[c]	37%
10	$[RhCpCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	46%
11	$PdCl_2(PPh_3)_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	—

Bold value signifies to highlight the optimal catalytic system.

[a] General reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), catalyst (5.0 mol %), additive (20–30 mol %), oxidant (0.5 mmol); DCE (2.0 mL), under ambient air; 100 °C, 20 h; Ar=4-MeOC$_6$H$_4$; yields of isolated products.

[b] Under an atmosphere of N$_2$.

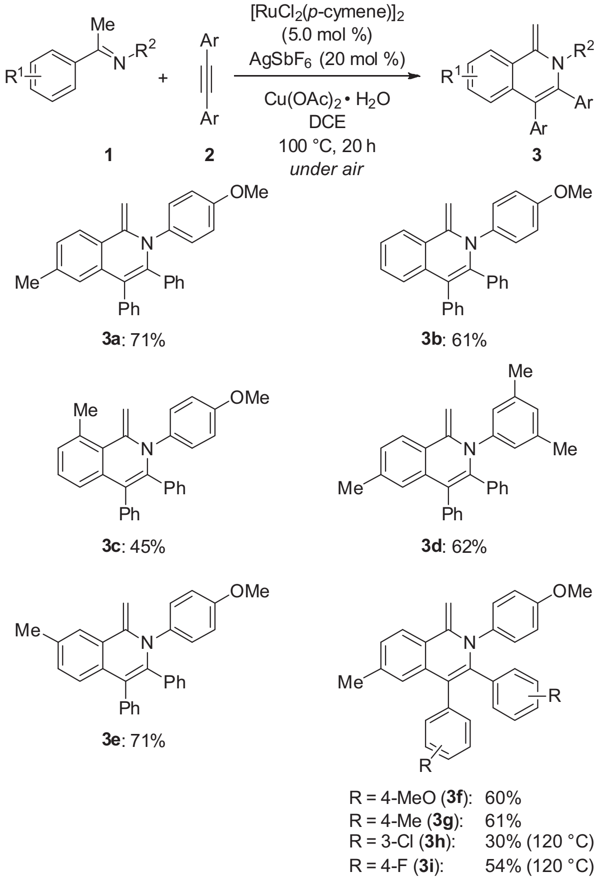
[c] MOAc (1.0 mmol).

2.2. Scope and limitations

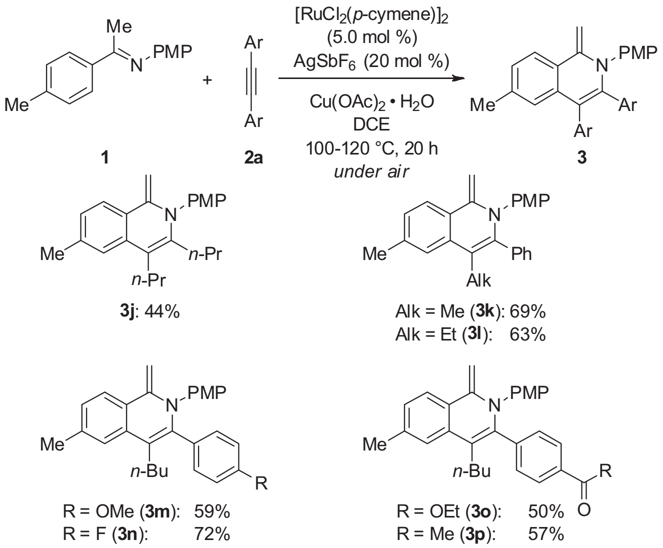
With an optimized catalytic system in hand, we tested its scope and limitations in the oxidative C–H bond functionalization with differently substituted ketimines **1** and alkynes **2** (Scheme 2). Hence, the oxidative annulation efficiently occurred with ketimines **1** displaying substituents on the *N*-aryl moiety. Notably, a more sterically hindered substrate bearing an *ortho*-methyl-substituent was also converted, albeit with a lower isolated yield of the product **3c**. A *meta*-decorated arene led to the site-selective C–H bond activation (**3e**), which can be rationalized in terms of significant steric interactions. Substituted tolane derivatives were found to be viable substrates as well, thereby delivering the desired products **3f–i**.

The optimized ruthenium(II) catalyst was not restricted to the use of diarylalkynes **2**, but proved to be applicable to alkyl-substituted starting materials as well (Scheme 3). Here, we particularly focused on the use of unsymmetrical substrates **2** to probe the challenging regiocontrol in the oxidative annulation. We were pleased to observe that the C–H bond functionalizations proceeded with excellent regioselectivities, placing the alkyl group distal to nitrogen. Furthermore, the ruthenium catalyst displayed a high chemoselectivity in which oxidative annulations of alkynes bearing an ester or a ketone group solely took place through chelation assistance by the ketimine moiety to furnish products **3o** and **3p**.

In order to access the corresponding reduced 1,2-dihydroisoquinolines **4** we subsequently devised a two-step reaction sequence consisting of the ruthenium-catalyzed C–H bond functionalization, along with a palladium-catalyzed hydrogenation (Scheme 4). The multicatalytic approach set the stage for the efficient preparation of the decorated products **4**, again occurring with excellent regio- and chemo-selectivities. It is noteworthy that a more sterically congested ketimine gave the ethyl-substituted dihydroisoquinoline **4c** in a comparable yield.



Scheme 2. Oxidative C–H functionalization with aromatic alkynes **2**.



Scheme 3. Oxidative C–H functionalization with aromatic alkynes **2**.

2.3. Mechanistic considerations

Given the unique features of our ruthenium-catalyzed C–H bond functionalization process, we performed mechanistic studies to delineate its mode of action. To this end, we performed competition experiments, which revealed arylalkynes to be preferentially converted (Scheme 5).