Tetrahedron 71 (2015) 2435–2441

Contents lists available at ScienceDirect

Tetrahedron

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

Rhodium-catalyzed mild and selective C–H allylation of indolines and indoles with 4-vinyl-1,3-dioxolan-2-one: facile access to indolic scaffolds with an allylic alcohol moiety

Satyasheel Sharma [a], Youngmi Shin [a], Neeraj Kumar Mishra [a], Jihye Park [a], Sangil Han [a], Taejoo Jeong [a], Yongguk Oh [a], Youngil Lee [b], Miji Choi [a], In Su Kim [a,*]

[a] School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea
[b] Department of Chemistry, University of Ulsan, Ulsan 680-749, Republic of Korea

ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form 12 February 2015
Accepted 13 February 2015
Available online 19 February 2015

Keywords:
Allylation
C–H Activation
Indole
Indoline
Rhodium

ABSTRACT

The rhodium(III)-catalyzed selective C–H allylations of indolines and indoles with 4-vinyl-1,3-dioxolan-2-one at room temperature are described. These transformations provide the direct and efficient formation of indolic scaffolds containing an allylic alcohol group.

1. Introduction

The functionalized allylic alcohols are important structural units found in a range of bioactive natural products and pharmaceuticals,[1] and are among the most useful synthetic precursors in organic and medicinal chemsitry.[2] Therefore, the incorporation of an allylic alcohol moiety into organic molecules has received great attention. The well-known method for the preparation of allylic alcohols is the nucleophilic ring-opening of vinyl epoxides with various organometallic reagents.[3] In addition, the Friedel–Crafts-type allylation of electron-rich arenes using vinyl epoxides was described.[4] However, these reactions usually suffer from the preparation of preactivated organometallic reagents, the production of hazardous byproducts, and harsh reaction conditions. An alternative catalytic protocol is the formation of π-allylpalladium species, derived from alkenyl oxiranes and Pd(0) catalysts, followed by nucleophilic addition of pronucleophiles.[5]

The transition-metal-catalyzed C–H bond functionalization has emerged as a powerful tool creating the intricate organic molecules due to its remarkable potential for step economy and environmental sustainability.[6] With the development of catalytic C–H bond functionalization, the direct C–H allylations have been achieved under various metal catalysis such as Rh,[7] Ir,[8] Ru,[9] Pd,[10] Re,[11] Cu,[12] Ni,[13] and Co[14] (Fig. 1). For instance, Glorius and Loh independently disclosed elegant examples on the Rh(III)-catalyzed allylation of benzamides with allylic carbonates or allylic acetates via olefin insertion and subsequent β-O-elimination pathway.[7a,c] In addition, Krische reported the Ir(I)-catalyzed allylation of benzamides using allenes as allyl sources.[8] Alternatively, our group demonstrated the Ru(II)-catalyzed terminal allylation of (hetero) aromatic and α,β-unsaturated carboxamides with allylic carbonates.[9b] Recently, Li described the beautiful studies on the Rh(III)-catalyzed C–H functionalization of arenes with strained *N*-Ts aziridines and vinyl oxiranes, leading to the formation of β-branched amines[15] and allylic alcohols.[16] Shortly thereafter, Wang successfully applied 4-vinyl-1,3-dioxolan-2-ones into aryl C–H allylation reaction under rhodium catalysis to deliver (*E*)-allylic alcohols on secondary benzamides.[17]

The C7- and C2-allylated indolic molecules are widely distributed in a large number of natural products and synthetic compounds with diverse biological activities.[18] Recently, the directing group-assisted catalytic C2-functionalizations of indoles[19] and C7-functionalizations of indolines[20] with various coupling partners have been demonstrated. In continuation of our recent study on the catalytic C–H bond functionalizations of indole C2-position[21] and

* Corresponding author. Tel.: +82 31 290 7788; fax: +82 31 292 8800; e-mail address: insukim@skku.edu (I.S. Kim).

http://dx.doi.org/10.1016/j.tet.2015.02.052
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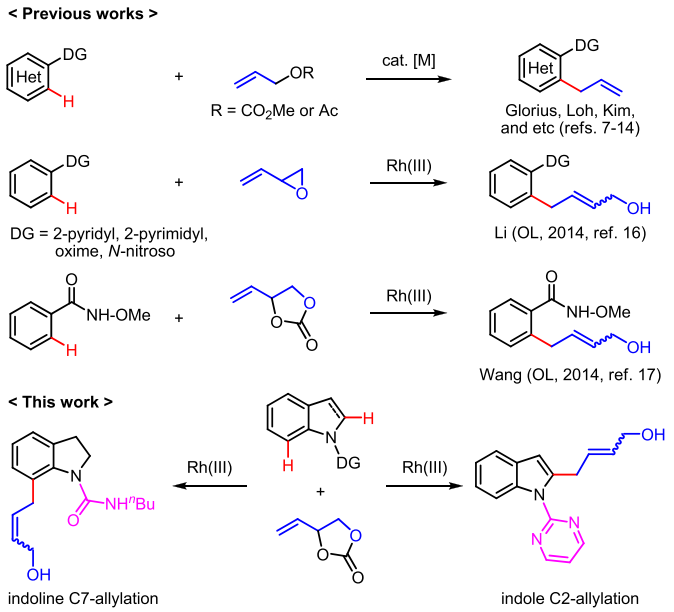


Fig. 1. Catalytic C–H allylations using allylic substrates.

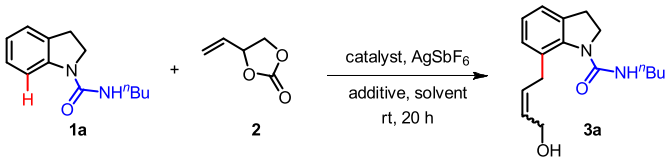
indoline C7-position,[22] we herein present the mild and selective rhodium-catalyzed direct C–H allylation of indolines and indoles with 4-vinyl-1,3-dioxolan-2-one, affording the corresponding indolic compounds containing an allylic alcohol group.

2. Results and discussion

Very recently, we reported the Rh(III)-catalyzed direct allylation of indolines with allyl methyl carbonate and γ-substituted allyl methyl carbonates to afford the corresponding allylation and crotylation products, where an *N*-butylcarbamoyl directing group is highly crucial for the formation of terminal olefination compounds without olefin migration.[22c] Thus indoline (**1a**) was selected as a starting material for optimizing C–H allylation with 4-vinyl-1,3-dioxolan-2-one (**2**). In initial study, cationic rhodium complex, derived from $[RhCp^*Cl_2]_2$ and $AgSbF_6$, in the presence of $Cu(OAc)_2$ additive in DCE solvent promoted the coupling of **1a** and **2** to provide allylated product **3a** in 52% yield with 5:1 of *Z*/*E* ratio (Table 1, entry 1). Interestingly, no migrated olefin (conjugated olefin) compound was observed, and other cationic ruthenium[9b] and cobalt[14] catalysts were found to be ineffective in this coupling reaction (Table 1, entries 2 and 3). Different solvent screening was carried out and *t*-AmOH was found to be the best solvent (Table 1, entries 4–6). However, the *Z*/*E* isomeric ratio of olefin was not altered in different solvents. Further screening of additive could not afford high yield and stereoselectivity (Table 1, entries 7 and 8). Fortunately, lowering amount of $Cu(OAc)_2$ to 30 mol % provided a slightly higher yield (83%) and selectivity (5:1) (Table 1, entry 10). However, no formation of **3a** was observed when either $Cu(OAc)_2$ or $AgSbF_6$ was excluded (Table 1, entries 11 and 12).

With the optimized reaction conditions in hand, the scope and limitations of indolines were examined (Table 2). First, various N-protecting groups **1b**–**1d** such as Ac, Piv, and Bz provided the moderate conversion yield and *Z*/*E* selectivity. The reaction of C4- and C5-substituted indolines **1e**–**1h** was found to undergo the allylation reaction to afford our desired products **3e**–**3h** in moderate to good yields. This reaction was also compatible with C6-substituted indolines **1i** and **1j** furnishing the corresponding products. In addition, C2- and C3-substituted indolines **1k**–**1o** displayed a good reactivity and selectivity under the present

Table 1
Selected optimization of reaction conditions[a]



Entry	Catalyst	Additive (mol %)	Solvent	Yield[b] (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (100)	DCE	52
2	$[Ru(p\text{-cymene})Cl_2]_2$	$Cu(OAc)_2$ (100)	DCE	14
3[c]	$CoCp^*COI_2$	$Cu(OAc)_2$ (100)	DCE	N.R.
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (100)	THF	50
5	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (100)	MeCN	14
6	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (100)	*t*-AmOH	76
7	$[RhCp^*Cl_2]_2$	CsOAc (100)	*t*-AmOH	8
8	$[RhCp^*Cl_2]_2$	PivOH (100)	*t*-AmOH	28
9	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (50)	*t*-AmOH	77
10	*$[RhCp^*Cl_2]_2$*	*$Cu(OAc)_2$ (30)*	*t-AmOH*	*83*
11	—	$Cu(OAc)_2$ (30)	*t*-AmOH	N.R.
12[d]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (30)	*t*-AmOH	Trace

[a] *Reaction conditions*: **1a** (0.2 mmol), **2** (0.4 mmol), catalyst (2.5 mol %), $AgSbF_6$ (10 mol %), additive (quantity noted), solvent (1 mL) under air at room temperature for 20 h in reaction tubes.
[b] Isolated yield by flash column chromatography, and all cases provided about 4:1 to 5:1 of *Z*/*E* isomeric ratio.
[c] Cobalt catalyst (5 mol %) was used.
[d] In the absence of $AgSbF_6$.

reaction conditions. It should be noted that all the reactions with indolines afforded the (*Z*)-isomers as major product, and no conjugated olefinic compound was observed by ^1H NMR analysis of crude reaction mixture. However, the C7-allylation of indoline **1p** containing 2-pyrimidinyl directing group resulted in high yield (81%), albeit in low *Z*/*E* selectivity (1:1.5). In addition, the scale-up reaction of **1a** was performed under lower loading (1.5 mol %) of Rh catalyst under otherwise identical conditions for 40 h to give a comparable yield (86%) of **3a** with a similar *Z*/*E* selectivity.

To further explore the allylation scope of indolic scaffold, we first tried to couple indole containing an *N*-butylcarbamoyl directing group with 4-vinyl-1,3-dioxolan-2-one (**2**) under the optimized conditions. Unfortunately, no formation of C7- or C2-allylation products was detected, and starting material with a cleavage of protecting group was observed.[21a,b] Thus we applied a 2-pyrimidinyl group known as an efficient directing group for C–H bond functionalization.[23] Interestingly, under the optimal reaction conditions (200 mol % of **2**), C2-allylated product **5a** was formed in 60% yield along with unexpected C2- and C7-bisallylated indole **6a** in 23% yield (Scheme 1a). In sharp contrast to indoline allylation products **3a**–**3o**, indoles **5a** and **6a** provided a high level of selectivity (*E*/*Z*=>20:1) for the formation of (*E*)-isomer. Decreasing amount of 4-vinyl-1,3-dioxolan-2-one (**2**) to 120 mol % furnished C2-allylated product **5a** in 55% yield, and a trace amount of **6a** was formed. It should be mentioned that no formation of only C7-mono-allylated indole was observed. Further the coupling of indoles **4b** and **4c** with 120 mol % of **2** provided C2-allylated products **5b** and **5c** in good yields with high *E*/*Z* selectivity (Scheme 1b). In addition, carbazole **4d** participated in catalytic allylation reaction to provide mono-allylated product **5d** in moderate yield (Scheme 1c). However, in the case of pyrrole **4e**, we were unable to control the mono-selectivity. Thus this reaction was performed using 200 mol % of **2** to give bis-allylation product **5e** in 65% yield with an *E*/*Z* ratio (>20:1) (Scheme 1d).

3. Conclusion

In conclusion, we have disclosed the mild and site-selective allylation reactions of indolines and indoles with 4-vinyl-1,3-