Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes for polycyclic heterocycles with four chiral stereogenic centers

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ARTICLE INFO

Article history:
Received 20 March 2015
Revised 14 May 2015
Accepted 19 May 2015
Available online xxxx

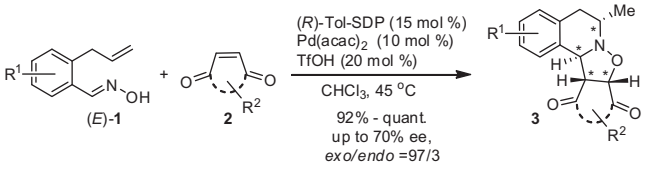
Keywords:
Stereoselective reaction
Domino reaction
Cyclization
Cycloaddition
Isoxazolidine

ABSTRACT

Diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes were established using a Pd(II)–(*R*)-Tol-SDP complex and triflic acid. The present process gave polycyclic heterocycles with four chiral stereogenic centers in almost quantitative yields and high stereoselectivities (up to 70% ee, *exo*/*endo* = 97/3).

The development of a facile construction of polycyclic heterocycles is a subject of intensive research because of their potential use in medicinal chemistry.[1,2] Among them, domino cyclization has become a powerful strategy for the formation of two or more rings in a single operation. In the domino cyclization, multiple chiral centers can often be formed with high stereoselectivities.[2] Nitrones derived from the reaction of oximes and alkenes are widely used 1,3-dipoles that endure cycloadditions with alkenes affording versatile isoxazolidine derivatives.[3] In 1994, Grigg et al. developed Pd(II)-catalyzed cyclization/cycloaddition cascade reaction of alkenyl oximes, effectively furnishing isoxazolidines with multiple stereocenters.[4] Despite the potential of this transformation, no enantioselective domino cyclization process has been reported.[5] Herein, we present the first enantioselective protocol of a cyclization/cycloaddition sequence of alkenyl oxime (*E*)-**1** with enedione **2** catalyzed by a Pd(II)–(*R*)-Tol-SDP complex and triflic acid (TfOH) (Scheme 1).

With the aim of developing a diastereoselective and enantioselective cyclization/cycloaddition sequence, the reaction of alkenyl oxime (*E*)-**1a** and *N*-methyl maleimide (**2a**) as prototypical substrates was attempted (Table 1).[4] Although a chiral complex derived from $PdCl_2(MeCN)_2$ with (*S*)-BINAP was used, no desired cyclic product **3a** was obtained. ESI-MS studies of the reaction



Scheme 1. Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reaction of alkenyl oxime **1** and enedione **2**.

indicated the formation of intermediate **4**.[4,6] To promote the protonolysis of the Pd–C bond in **4** that lead to the domino process, various Brϕnsted acids as proton sources were employed. Among the acids tested ($HClO_4$, HCl_{aq}, *p*-Tol-SO_3H, CF_3CO_2H, *o*-NO_2–C_6H_4–CO_2H, HCO_2H, and AcOH), the addition of TfOH was found to promote the domino process effectively, resulting in the formation of **3a** with 70% yields in the ratio of *exo*/*endo*-**3a** to 93/7; the *exo*-cycloadduct **3a** was obtained as a major product in 37% enantiomeric excess (ee) (entry 2). Encouraged by these results, we further studied the effects of other reaction conditions such as solvents, Pd salts, a ratio of substrates, and temperature. The use of $CHCl_3$ as a reaction solvent resulted in the formation of **3a** with 46% ee (entry 4). Chiral Pd complexes prepared from $Pd(acac)_2$ with (*S*)-BINAP were found to give **3a** in higher enantioselectivity (55% ee, entry 7) than those prepared from other Pd salts. The optimal result (quant, *exo*/*endo* = 93/7, 56% ee) with

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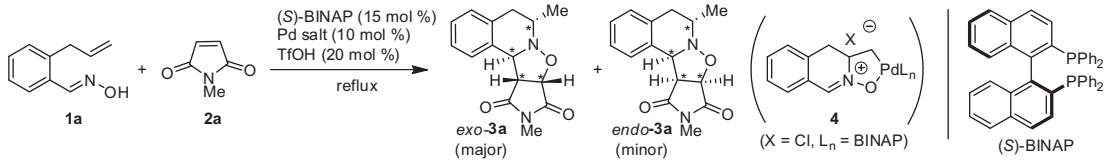
http://dx.doi.org/10.1016/j.tetlet.2015.05.070
0040-4039/

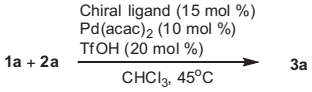
Table 1
Screening of reaction conditions[a]



Entry	Pd salt	Ratio (**1a**:**2a**)	Solvent	Time (h)	Total yields of **3a** (%)[a]	Ratio of *exo*/*endo*-**3a**[b]	ee of *exo*-**3a** (%)[b]
1	$PdCl_2(MeCN)_2$	1:1	CH_2Cl_2	24	Trace[c]	–	–
2	$PdCl_2(MeCN)_2$	1:1	CH_2Cl_2	12	70	93/7	37
3	$PdCl_2(MeCN)_2$	1:1	THF	6	64	91/9	37
4	$PdCl_2(MeCN)_2$	1:1	$CHCl_3$	6	60	92/8	46
5	$PdCl_2(PhCN)_2$	1:1	$CHCl_3$	6	79	90/10	47
6	$PdCl_2(COD)$	1:1	$CHCl_3$	6	85	91/9	46
7	$Pd(acac)_2$	1:1	$CHCl_3$	6	67	91/9	55
8	$Pd(acac)_2$	1:2	$CHCl_3$	6	36	92/8	41
9	$Pd(acac)_2$	2:1	$CHCl_3$	6	83	91/9	46
10[d]	$Pd(acac)_2$	2:1	$CHCl_3$	10	Quant	93/7	56

[a] Isolated yield.
[b] Determined by HPLC.
[c] In the absence of TfOH.
[d] At 45 °C.

Table 2
Screening of chiral ligands[a]



Entry	Chiral ligand	Time (h)	Total yields of **3a** (%)[a]	Ratio of *exo*/*endo*-**3a** (%)[b]	ee of *exo*-**3a** (%)[b]
1	(*S*)-Tol-BINAP	10	94	92:8	46
2	(*R*)-C_3-Tunephos	15	43	92:8	−55[c]
3	(*R*)-Segphos	15	Quant	92:8	−58[c]
4	(*R*)-SDP	8	72	92:8	62
5	(*R*)-Tol-SDP	8	Quant	94:6	70
6	(*R*)-Xyl-SDP	8	Quant	90:10	48
7	(*S*)-MOP	15	78	93:7	0
8	(*S*,*S*)-*t*-Bu-BOX	12	78	93:7	0
9	(*P*,*R*,*R*)-*i*-Pr-SPRIX	12	92	90:10	4

[a] Isolated yield.
[b] determined by HPLC.
[c] Opposite enantiomer was obtained.