Organic LETTERS

Letter

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Catalyst-Controlled Amino- versus Oxy-Acetoxylation of Urea-Tethered Alkenes: Efficient Synthesis of Cyclic Ureas and Isoureas

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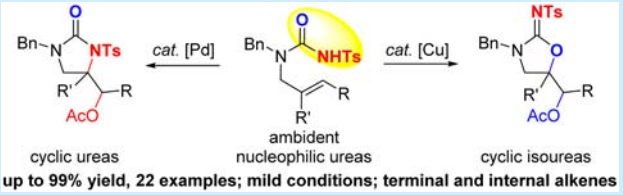
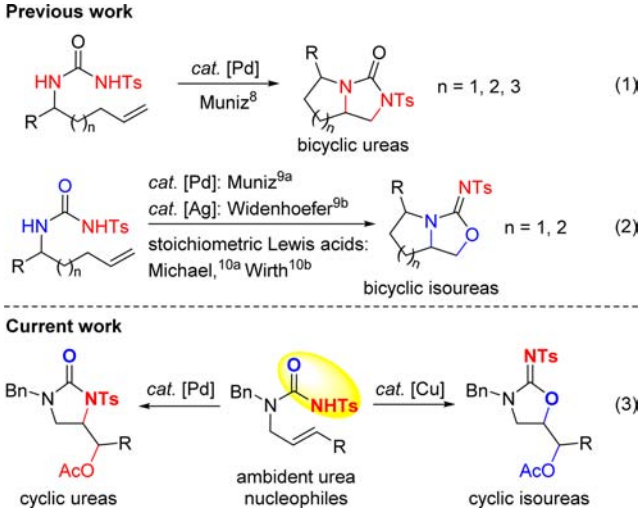
Supporting Information

ABSTRACT: A catalyst-controlled vicinal amino- versus oxy-acetoxylation of alkenes with $PhI(OAc)_2$ as the oxidant is described. The divergent synthesis of cyclic ureas and isoureas was achieved in good yields under mild conditions employing ambident urea nucleophiles. Both terminal and internal alkenes are compatible with this reaction protocol.



Vicinal difunctionalization of alkenes represents a powerful tool in the field of organic synthesis. Among these difunctionalization methods is the pioneering work, the well-known Sharpless asymmetric aminohydroxylation[1] and dihydroxylation.[2] Inspired by these works, great efforts have been devoted to transition-metal-catalyzed vicinal difunctionalization of alkenes and great advances have been achieved in the past several decades.[3−7] In 2005, the Muñiz group reported the first Pd-catalyzed intramolecular diamination of unfunctionalized alkenes with modified ureas as nitrogen sources to the synthesis of bicylic ureas (eq 1).[8] Intramolecular amino-oxylation of



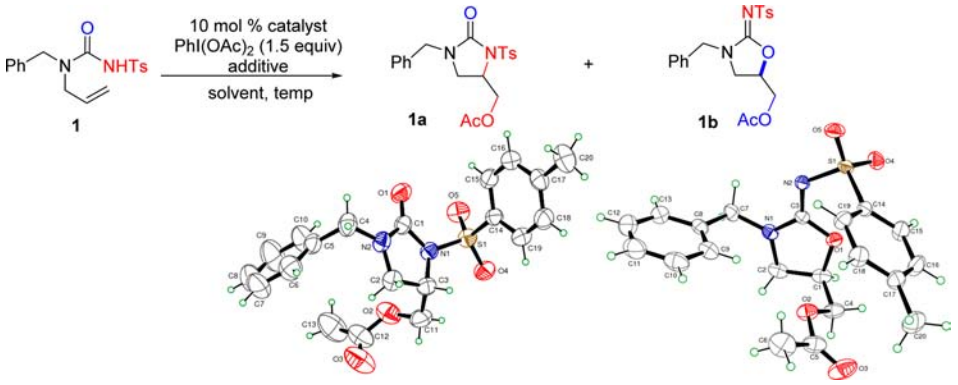
alkenes for the synthesis of bicyclic isoureas has also been achieved by the use of a catalytic amount of Pt,[9a] Ag,[9b] or excess amount of Lewis acid[10] (eq 2). However, the resulting products were limited to fused bicycles, and the reactions relied on the use of expensive Pt or Ag catalysts or were operated under −78 °C in the presence of excess strong Lewis acids. Moreover, the divergent synthesis of these two heterocylces via controllable O/N nucleophilic functionalization of alkenes from ambident urea nucleophiles have not been reported.[11,12] Cyclic ureas and isoureas are two biologically important heterocycles widely found in natural products and pharmaceuticals.[13] In addition, they are also valuable intermediates in various organic transformations and precursors to 1,2-diamines and 1,2-aminoalcohols.[14] Consequently, development of efficient methods for access to these heterocycles is of significant importance in organic synthesis. Herein, we would like to address this challenge and report a catalyst-controlled intramolecular amino- versus oxy-acetoxylation of urea-tethered alkenes under mild conditions. This protocol allows the chemoselective construction of a broad range of cyclic ureas and isoureas in high yields from ambident urea nucleophiles (eq 3).

We initiated our investigations with the difunctionalization of alkene in *N*-allylic urea **1** using $PhI(OAc)_2$ as the oxidant, because ureas are ambident O/N nucelophiles.[11,12] After extensive screenings, we were pleased to find that the optimized reaction conditions for aminoacetoxylation was obtained when $Pd(OAc)_2$ was used as the catalyst in HOAc at room temperature (Table 1, entry 1, 99% **1a**).[4h] Notably, the cyclic **1a** was exclusively obtained and **1b** was completely inhibited under the reaction conditions. It was found that both $Pd(OAc)_2$ and HOAc were necessary for the successful transformation (entries 2−5). Other organic acids including $PhCO_2H$, PivOH, and (*R*)-BINOL-PO_2H were also tested, but the outcomes were very disappointing (entries 6−8). Simultaneously, the oxy-acetoxylation product **1b** was exclusively obtained in 99% yield with 10 mol % $Cu(MeCN)_4PF_6$ and DCM/HOAc as the solvent under 40 °C as the optimized reaction conditions (entry 9). A controlled experiment showed that the oxy-acetoxylation reaction could not take place in the absence of $Cu(MeCN)_4PF_6$ (entry 10). HOAc was crucial for the reaction, since no product was observed in the absence of HOAc (entry 11). It was found that $Cu(OTf)_2$ was able to catalyze the reaction to afford **1b** in 80% yield (entry 12). Finally, the structures of amino-acetoxylation product **1a** and oxy-

Received: June 16, 2015
Published: July 13, 2015

DOI: 10.1021/acs.orglett.5b01741
Org. Lett. 2015, 17, 3758−3761

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive	solvent	temp (°C)	yield of **1a** (%)[b]	yield of **1b** (%)[b]
1	**$Pd(OAc)_2$**		**HOAc**	**rt**	**99**	**0**
2[c]	/		HOAc	rt	–	–
3	$Pd(OAc)_2$		DCM/HOAc (v/v = 3:1)	rt	78	0
4	$Pd(OAc)_2$		DCM	rt	–	–
5	$Pd(OAc)_2$		MeCN	rt	–	–
6	$Pd(OAc)_2$	$PhCO_2H$ (1.0 equiv)	DCM	rt	trace	0
7	$Pd(OAc)_2$	PivOH (1.0 equiv)	DCM	rt	trace	0
8	$Pd(OAc)_2$	(*R*)-BINOL-PO_2H (1.0 equiv)	DCM	rt	12	0
9	**$Cu(MeCN)_4PF_6$**		**DCM/HOAc (v/v = 3:1)**	**40**	**0**	**99**
10[c]			DCM/HOAc (v/v = 3:1)	40	–	–
11	$Cu(MeCN)_4PF_6$		DCM	40	–	–
12	$Cu(OTf)_2$		DCM/HOAc (v/v = 3:1)	40	0	80

[a]Reaction conditions: Substrate **1** (0.2 mmol), Pd or Cu catalyst (10 mol %), and $PhI(OAc)_2$ (0.3 mmol, 1.5 equiv) in solvent (2 mL) under the corresponding temperature for 12 h. [b]Isolated yield. [c]24 h, almost no conversion.

acetoxylation product **1b** were unambiguously confirmed by X-ray crystallography.[15]

With the optimized conditions in hand, the substrate scope was examined on the palladium-catalyzed amino-acetoxylation of alkenes as shown in Figure 1. Several substrates bearing functional groups, such as trifluoromethyl (**3a**) and fluoro (**4a**), could proceed smoothly in the catalytic system. It is worth noting that when synthetically useful protecting group Cbz was used, the corresponding product **5a** was also isolated in 52% yield. Significantly, both *trans*- and *cis*-urea-tethered alkenes bearing a phenyl group were decent substrates to afford the corresponding product **6a** in 94% yield and 87% yield, respectively, but suffered from a poor *dr* ratio. The urea-tethered alkene bearing (*p*-CF_3)Ph group could also undergo the palladium-catalyzed amino-acetoxylation to afford the 5-*exo*-cyclization product **7a** in 65% yield. Meanwhile, when the substrate derived from easily accessible L-proline was employed, the desired bicyclic product **8a** was obtained in 44% yield. Further investigation revealed that *cis*-alkene with a methyl group on its terminal site gave the terminal alkene **9a** in 32% yield instead of the amino-acetoxylation product, presumably due to the faster β-H elimination over the oxidation of the Pd(II)-intermediate with $PhI(OAc)_2$. A 2,2-disubstituted alkene could also undergo the cyclization, albeit with poor regioselectivity, affording both the 5-*exo*-cyclization product (**10a**, 30%) and 6-*endo*-cyclization product (**10aa**, 45%). When a 2,2-disubstituted alkene bearing a phenyl group was examined, the cyclization reaction not only afforded the 6-*endo*-cyclization product **11a** but also the β-H elimination product **11aa**.

Subsequently, the substrate scope was also examined on the copper-catalyzed oxy-acetoxylation of alkenes as shown in Figure 2. 2,2-Disubstituted alkenes could react smoothly and exclusively gave the 5-*exo*-cyclization isourea **5b** (77%) and **6b** (80%), regardless of bearing a methyl or phenyl group. We

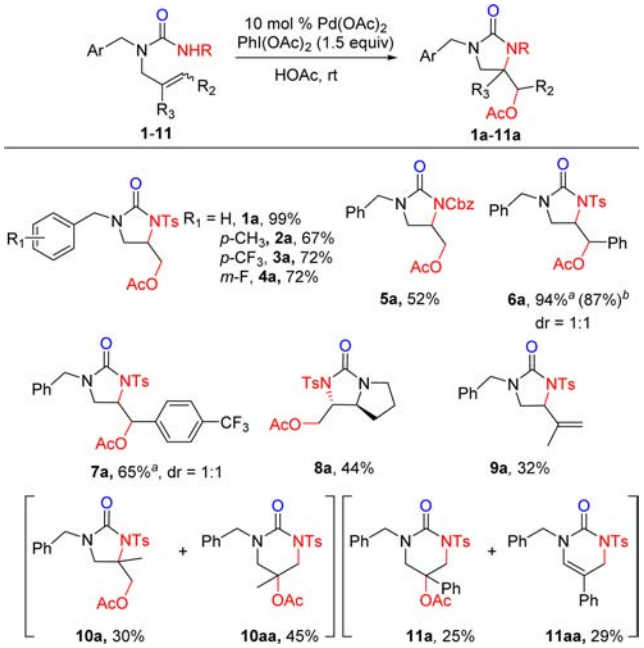


Figure 1. Substrate scope for palladium-catalyzed amino-acetoxylation. Reaction conditions: substrates (0.5 mmol), $Pd(OAc)_2$ (10 mol %), and $PhI(OAc)_2$ (1.5 equiv) in HOAc (0.1 M) at rt for 12 h. Isolated yield. The dr ratio was determined by ^1H NMR analysis. [a] Yield from *trans*-alkene. [b] Yield from *cis*-alkene.

DOI: 10.1021/acs.orglett.5b01741
Org. Lett. 2015, 17, 3758–3761

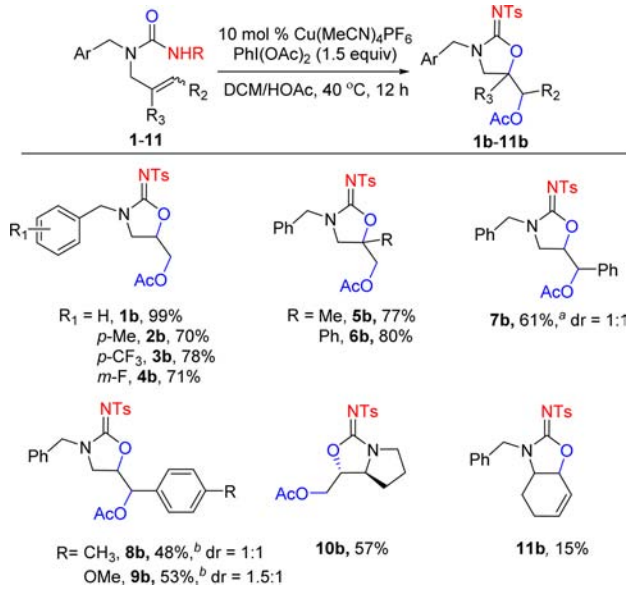


Figure 2. Substrate scope for copper-catalyzed oxy-acetoxylation. Reaction conditions: Substrates (0.5 mmol), $Cu(MeCN)_4PF_6$ (10 mol %), and $PhI(OAc)_2$ (1.5 equiv) in DCM/HOAc (0.1 M; v/v = 3:1) at 40 °C for 12 h. Isolated yield. [a] Yield from *cis*-alkene. [b] Yield from *trans*-alkene.

discovered that 1,2-disubsitued alkenes bearing phenyl, (*p*-Me)Ph, and (*p*-OMe)Ph also reacted smoothly under the optimized conditions, exclusively affording the corresponding isourea **7b**, **8b**, and **9b** in moderate yields. Bicyclic isourea **10b** could also be obtained in moderate yield via copper-catalyzed oxy-acetoxylation. However, urea-tethered cyclohexene appeared to be an ineffective substrate and the *β*-H elimilation product **11b** instead of the oxy-acetoxylation product was isolated in poor yield.

Moreover, both the Pd-catalyzed amino-acetoxylation and Cu-catalyzed oxy-acetoxylation reactions could be scaled up to 10 mmol scale as shown in Scheme 1. The urea-type product **1a** was obtained in 91% yield even when the amount of $Pd(OAc)_2$ was lowered to 5 mol %, and isourea-type product **1b** was also obtained in 84% yield.

Scheme 1. Large-Scale Divergent Synthesis

In conclusion, we have developed a catalyst-controlled intramolecular amino- versus oxy-acetoxylation of *N*-allyl ureas under mild conditions. This protocol allows the chemoselective construction of a broad range of cyclic ureas and isoureas in high yields from ambident urea nucleophiles. Both terminal and internal alkenes are compatible with this reaction protocol. In addition, the divergent synthesis of cyclic ureas and isoureas could be scaled up to 10 mmol scale. Our current efforts focused on the synthetic application in complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds, and X-ray crystallography/CIF for **1a** and **1b**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01741.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Basic Research Program of China (2015CB856600), the NSFC (21422206, 21272206), and the Fundamental Research Funds for the Central Universities is gratefully acknowledged.

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(15) CCDC 949100 (**1a**) and 959091 (**1b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.orglett.5b01741
Org. Lett. 2015, 17, 3758−3761