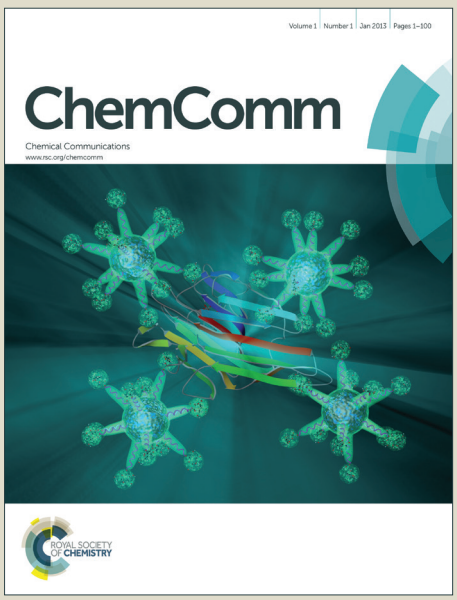
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Expedient Access to Substituted 3-Amino-2-cyclopentenones By Dirhodium-catalyzed [3+2]-Annulation of Silylated Ketene Imines and Enoldiazoacetates

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

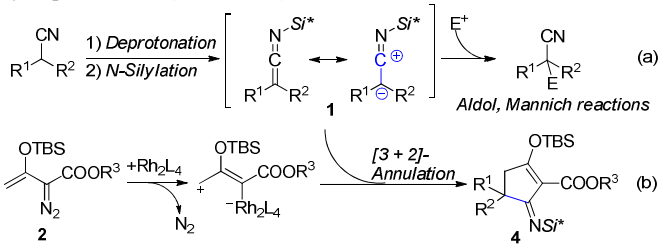
www.rsc.org/

Xichen Xu, John S. Leszczynski, Savannah M. Mason, Peter Y. Zavalij and Michael P. Doyle*

In a reaction that proceeds under mild conditions with remarkable functional group tolerance, structurally diverse 3-amino-2-cyclopentenones bearing a quaternary carbon at the 4-position have been synthesized through a formal [3+2]-cycloaddition reaction of silylated ketene imines (SKIs) and enoldiazoaceates by dirhodium catalysis.

Cyclopentenones are ubiquitous structural frameworks of natural products and important pharmaceuticals.[1] Both simple and highly functionalized cyclopentenones serve as building blocks for the construction of complex molecular architectures.[2] The Nazarov cyclization[3] and the Pauson-Khand reaction[4] constitute powerful approaches for the synthesis of cyclopentenones. However, the need to use a stoichiometric amount of activator,[3,4] the availability of starting materials[3] and the often harsh reaction conditions[3] have limited the practicality of these methods. Recently, transition metal catalyzed annulation approaches to functionalized cyclopentenones have been reported,[5] but the reported methods also have structural limitations; and none of them introduces an amino functional group into the product. Silylated ketene imines (SKIs),[6] generated by the deprotonation and subsequent *N*-silylation of α-branched nitriles, are nucleophiles that can react with electrophilic counterparts to form a quaternary carbon center under Lewis acid[7] or base[8] catalysis (Scheme 1a); and, possibly due to the unique placement of a silyl group at the *N*-terminus, SKIs rarely undergo cycloaddition reactions,[9] which is in sharp contrast to their ketene and ketene imine analogues.[10] However, the potential of SKIs to serve as dipole acceptors in such transformations has not been explored.

We have been interested in the transformations of electrophilic rhodium carbene intermediates derived from silylated enoldiazoacetates that have recently been demonstrated to undergo [3+3]-cycloaddition with a variety of 1,3-dipolar species.[11] The chemistry of nucelophilic SKIs in combination with catalytically generated electrophilic metallated 1,3-dipole equivalents has not, to our knowledge, been previously documented.[10] Herein, we report a highly efficient protocol for the assembly of enoldiazoacetates and SKIs under dirhodium catalysis to produce substituted 3-amino-2-cyclopentenones (Scheme 1b).

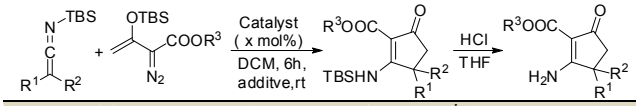


Scheme 1. (a) SKIs as nucleophiles. (b) Formal [3+2]-cycloaddition of SKIs **1** and enoldiazoacetate **2**.

Our investigation was initiated by controlled addition of a solution of enoldiazoacetate **2a** to the mixture of dirhodium catalyst and SKI **1a** in dichloromethane at room temperature. By monitoring the reaction progress via TLC analysis and ^{1}H NMR spectroscopy, the consumption of SKI **1a** and the formation of a new product **3a** (eq 1), whose structure was assigned by spectroscopic analysis to have originated from [3+2]-annulation, was observed. But the isolated yield of **3a** was very low (<10%) and the hydrolysis of SKI **1a** to the parent nitrile dominated. Adding activated 4Å MS to the reaction system dramatically increased the reaction yield by suppressing the proton desilylation of SKI **1a,** and the TBS-protected 3-amino-2-cyclopentenone **3a** was produced in excellent yield (Table 1, entry 2). Treatment of **3a** with a catalytic amount of aqueous HCl in THF cleaved the Si-N bond and provided the desilylated 3-amino-2-cyclopentenone product **4a** in quantitative yield. While the less soluble $Rh_2(OAc)_4$ gave a slightly lower product yield than did $Rh_2(Oct)_4$ (entry 3), $Rh_2(OPiv)_4$ with its sterically encumbered ligands was much less effective (entry 4). The more Lewis acidic catalyst $Rh_2(TFA)_4$ (entry 5), which was probably deactivated by the Lewis basic SKI **1a**,[12] only generated a trace amount of **3a**. The less Lewis acidic $Rh_2(Cap)_4$ did not catalyze the cycloaddition reaction, even at 80 °C in 1,2-dichloroethane (entry 6). Use of

other transition metal catalysts, including $Cu(OTf)_2$ (entry 7) and $AgSbF_6$ (entry 8), only resulted in complex product mixtures under otherwise identical conditions without forming **3a**. The Lewis acid $Sc(OTf)_3$ showed no catalytic reactivity (entry 9).

Table 1. Optimization for the [3+2]-cycloaddition reaction.

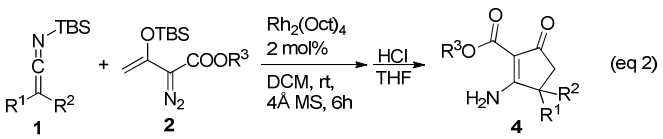


Entry[a]	Catalyst	Mol%	Additive[b]	Yield of **3a**[c]
1	$Rh_2(Oct)_4$	2 mol%	none	<10%
2	$Rh_2(Oct)_4$	2 mol%	4Å MS	91%
3	$Rh_2(OAc)_4$	2 mol%	4Å MS	87%
4	$Rh_2(OPiv)_4$	2 mol%	4Å MS	45%
5	$Rh_2(TFA)_4$	2 mol%	4Å MS	<10%
6[d]	$Rh_2(Cap)_4$	2 mol%	4Å MS	<5%
7	$Cu(OTf)_2$	5 mol%	4Å MS	<5%
8	$AgSbF_6$	5 mol%	4Å MS	<5%
9	$Sc(OTf)_3$	5 mol%	4Å MS	No reaction

[a]Reactions were performed on 0.4 mmol of SKI **1a** (1.0 equivalent). Enoldiazoacetate **2a** (1.1 equivalent) in dichloromethane was added via syringe pump over 30 mins. [b]4Å MS was activated prior to use. See ESI for detail. [c]Isolated product yield after chromatography. [d]Reaction performed at 80 °C in 1,2-dichloroethane.

Having identified the optimal reaction condition, we surveyed a diverse array of substrates to test the generality of this formal [3+2]-cycloaddition strategy, and results from this investigation are reported in Table 2. Changing of the ester substitutent of the enoldiazoacetate from methyl (entry 1) to benzyl (entry 2) shows minimal impact on the reaction outcome, and the resulting benzyl ester product was obtained in comparable reaction yield. Single crystal X-ray analysis of **4b** confirmed our structural assignment (Figure 1). Different aryl and alkyl substituents of the SKIs are well tolerated. Replacing the methyl group of SKI **1a** with an ethyl group (entry 3) showed marginal influence on the reaction yield. However, replacement of the methyl group with an isopropyl group (entry 4) significantly lowered reaction yield. An SKI with an allyl group attached to the terminal carbon was also compatible with the reaction condition, and no cyclopropanation product was observed (entry 5). Substituents with distinctive electronic properties on the phenyl ring were accommodated as well (entries 6-9). A SKI bearing a naphthyl instead of a phenyl group also underwent reaction (entry 10). Finally, SKIs derived from diphenylacetonitrile (entry 11) and cyclohexanecarbonitrile (entry 12) participated in the reaction and afforded the corresponding products in good yields. Overall, the [3+2]-annulation methodology represents a general approach for introducing a quaternary carbon onto the 3-amino-2-cyclopentenone skeleton.

Table 2. Substrate scope for the formal [3+2]-cycloaddition reaction.



1 2 4

Entry[a]	**4**	R^1	R^2	R^3	Yield[b,c]
1	**4a**	Me	Ph	Me	91%
2	**4b**	Me	Ph	Bn	90%
3	**4c**	Et	Ph	Me	88%
4	**4d**	*i*-Pr	Ph	Me	54%
5	**4e**	Allyl	Ph	Me	65%
6	**4f**	Me	4-$MeOC_6H_4$	Me	63%
7	**4g**	Me	4-ClC_6H_4	Me	83%
8	**4h**	Me	3-ClC_6H_4	Me	85%
9	**4i**	Me	3-$MeOOCC_6H_4$	Me	65%
10	**4j**	Me	2-Naphthyl	Me	67%
11	**4k**	Ph	Ph	Me	70%
12	**4l**	R^1,R^2 = -$(CH_2)_4$-		Me	56%

[a]Reactions were performed on 0.4 mmol of SKI **1a** (1.0 equivalent). Enoldiazoacetate **2a** (1.1 equivalent) in dichloromethane was added via syringe pump over 30 mins. [b]Isolated reaction yield. [c]Reaction performed on 1.0 gram scale of **1a** afforded **4a** in comparable reaction yield (87%).

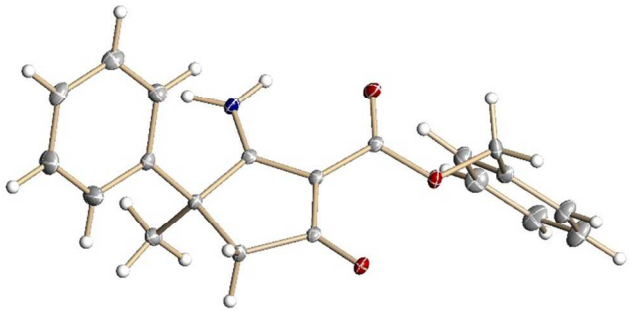
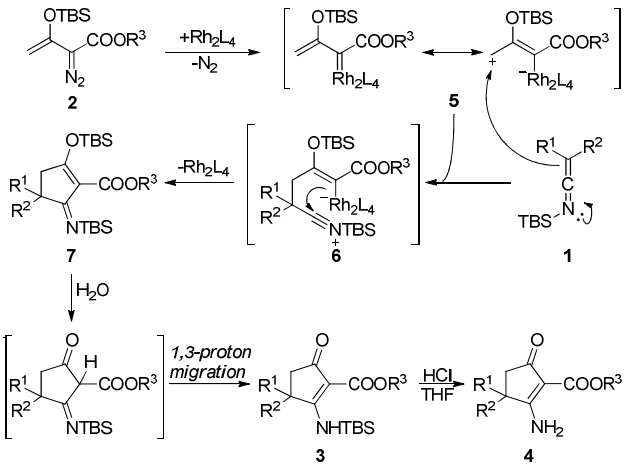


Figure 1. X-ray crystal structure of **4b** and CCDC 965494 contains the supplementary crystallographic data. Thermal ellipsoids set at a 30% probability.

The unusual outcome of the dirhodium(II)-catalyzed reaction is consistent with the mechanism that is outlined in Scheme 3. Dirhodium-catalyzed dinitrogen extrusion from **2** forms the electrophilic rhodium carbene intermediate **5** that preferentially undergoes vinylogous electrophilic addition to form nitrilium ion intermediate **6**. Intramolecular nitrilium ion addition to the nucleophilic vinylrhodium carbon center with release of the catalyst forms cyclopentane-imine **7**. The cyclopentane-imine **7** appears to be highly unstable and undergoes facile hydrolysis and subsequent 1,3-proton transfer reaction to yield the TBS-protected 3-amino-2-cyclopentenone **3**. In a control experiment, triisopropylsilyl (TIPS)-substituted enoldiazoacetate **2c** engaged in the [3+2]-cycloaddition reaction and provided the identical TBS-substituted 3-amino-2-cyclopentenone **3**. The result concludes that the hydrolysis of **7** occurs exclusively from the oxygen rather than from the nitrogen.

Upon treating the product **3a** with a catalytic amount of HCl, the 3-amino-2-cyclopentenone **4** is generated.



Scheme 3. The proposed mechanism for the [3+2]-annulation reaction.

This [3+2]-cyclization compliments a recent report by Davies and coworkers for reactions of enoldiazoacetates with silylated enol ethers that involve vinylogous oxonium ion addition to the intermediate metal carbene, but in their case ring closure requires a bulky substituent on the vinyl ether to prevent OTBS transfer that forms propargylic product.[13]

In conclusion we have discovered a catalytic [3+2]-cycloaddition reaction of SKIs and enoldiazoacetates with catalysis by dirhodium(II) carboxylates. This protocol offers convenient access to substituted 3-amino-2-cyclopentenones having quaternary chiral centers at the 4-position. The development of the asymmetric variant of this reaction is underway.[14]

We are grateful to the National Science Foundation (CHE-0946988) for their support of this research.

Notes and references

Department of Chemistry and Biochemistry, University of Maryland, College Park, MD, 20740, USA.

Electronic Supplementary Information (ESI) available: [experimental procedures and characterization data of new compounds and copies of NMR spectra]. See DOI: 10.1039/c000000x/

1 (a) F. Marks, G. Fürstenberger. Prostaglandins, Leukotrienes and Other Eicosanoids. From Biogenesis to Clinical Application; Wiley-VCH, **1999**. (a) D. S. Straus, C. K. Glass, *Medical Research Reviews* **2001**, *21*, 185. (b) S. M. Roberts, M. G. Santoro, E. S. Sickle, *J. Chem. Soc., Perkin Trans 1* **2002**, 1735.

2 (a) F. Rezgui, H. Amrib, M. M. E. Gaïed, *Tetrahedron* **2003**, 1369.

3 (a) M. A. Tius, *Acc. Chem. Res.* **2003**, *36*, 284. (b) V. B. Kurteva, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 6809. (c) T. N. Grant, C. J. Rieder, F. G. West, *Chem. Commun.* **2009**, *45*, 5676. (d) M. Harmata, *Chem. Commun.* **2010**, *46*, 8886.

4 (a) N. E. Schore, *Org. React.* **1991**, *40*, 1. (b) K. M. Brummond, J. L. Kent, *Tetrahedron* **2000**, *56*, 3263. (c) S. E. Gibson, A. Stevenazzi, *Angew. Chem. Int. Ed.* **2003**, *42*, 1800. (d) S. E. Gibson, N. Mainolfi, *Angew. Chem. Int. Ed.* **2005**, *44*, 3022. (e) L. V. R. Reddy, V. Kumar, R. Sagar, A. K. Shaw, *Chem. Rev.* **2013**, *113*, 3605.

5 (a) J. Barluenga, P. Barrio, L. Riesgo, L. A. López, M. Tomás, *J. Am. Chem. Soc.* **2007**, *129*, 14422. (b) C. P. Davie, R. L. Danheiser, *Angew. Chem. Int. Ed.* **2005**, *44*, 5867. (c) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802. (d) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442. (e) A. D. Jenkins, A. Herath, M. Song, J. Montgomery, *J. Am. Chem. Soc.* **2011**, *133*, 14460.

6 (a) S. E. Denmark, T. W. Wilson, *Angew. Chem. Int. Ed.* **2012**, *51*, 9980. (b) P. Lu, Y. Wang, *Chem. Soc. Rev.* **2012**, *41*, 5687. (c) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086.

7 J. Zhao, X. Liu, W. Luo, M. Xie, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2013**, *52*, 3473.

8 (a) S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405. (b) S. E. Denmark, J. R. Heemstra, Jr., *Org. Lett.* **2003**, *5*, 2303. (c) S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774. (d) A. H. Mermerian, G. C. Fu, *Angew. Chem. Int. Ed.* **2005**, *44*, 949. (e) S. E. Denmark, T. W. Wilson, M. T. Burk, J. R. Heemstra, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 14864. (f) G. T. Notte, J. M. B. Vu, J. L. Leighton, *Org. Lett.* **2011**, *13*, 816.

9 Allyl group tethered SKIs undergoes formal [4+2]-cycloaddition: (a) J. L. Alonso-Gómez, Y. Pazos, A. Navarro-Vázquez, J. Lugtenburg, M. M. Cid, *Org. Lett.* **2005**, *7*, 3773. (b) A. Navarro-Vázquez, J. Alonso- Gómez, J. Lugtenburg, M. M. Cid, *Tetrahedron* **2010**, *66*, 3855.

10 A. D. Allen, T. T. Tidwell, *Chem. Rev.* **2013**, *113*, 7287.

11 (a) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402. (b) X. Xu, M. O. Ratnikov, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2011**, *13*, 6122. (c) Y. Qian, X. Xu, X. Wang, P. Y. Zavalij, W. Hu, M. P. Doyle, *Angew. Chem. Int. Ed.* **2012**, *51*, 5900. (d) X. Xu, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9829. (e) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle, *Chem. Commun.* **2012**, *48*, 11522. (f) X. Xu, D. Shabashov, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2012**, *14*, 800. (g) X. Wang, Q. M. Abrahams, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2012**, *51*, 5907. (h) X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 12439.

12 Intense color change from green to yellow occurred when SKI **1a** was mixed with $Rh_2(TFA)_4$ in dichloromethane at room temperature.

13 A. G. Smith, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 18241.

14 Preliminary result suggests that 42% ee for **4a** can be achieved with catalysis by Rh_2(*S*-PTTL)$_4$ in toluene at room temperature.

Journal Name RSCPublishing

COMMUNICATION

TOC

3-Amino-2-cyclopentenones with a quaternary carbon at the 4-position from formal [3+2]-cycloaddition of silylated ketene imines (SKIs) and enoldiazoaceates by dirhodium catalysis.