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Au-Catalyzed Synthesis of 5,6-Dihydro-8*H*-indolizin-7-ones from *N*-(Pent-2-en-4-ynyl)-*β*-lactams

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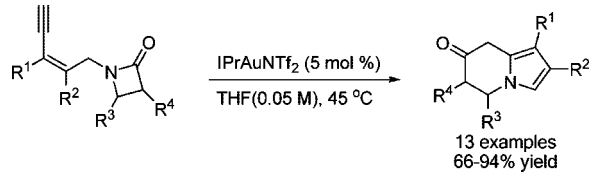
ABSTRACT

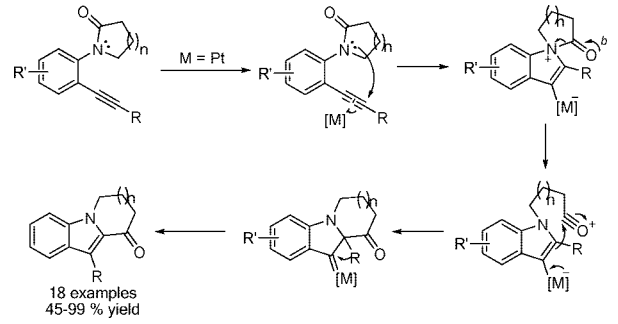


Au-catalyzed synthesis of 5,6-dihydro-8*H*-indolizin-7-ones from readily available *N*-(pent-2-en-4-ynyl)-*β*-lactams is developed. In this reaction, a *5-exo-dig* cyclization of the *β*-lactam nitrogen to the Au-activated C−C triple bond is followed by heterolytic fragmentation of the amide bond, forming a highly nucleophilic acyl cation. An expedient formal synthesis of indolizidine 167B was easily achieved using this new method.

In the past few years, Au catalysis[1] has rapidly evolved from a relatively unknown phenomenon into an established area in organic synthesis. Various practical synthetic methods have been developed.

We reported previously that *N*-(2-alkynylaryl)lactams underwent two consecutive 1,2-migrations in the presence of $PtCl_4$ or $PtCl_2$, yielding cyclic ketone-fused indoles (Scheme 1).[2] Au(I) also catalyzed this reaction albeit less efficient. This reaction was proposed to undergo an initial *5-endo-dig* cyclization of the lactam nitrogen to the metal-activated alkyne followed by the fragmentation of the lactam amide bond and the formation of an acyl cation.[3] The benzene ring in the substrate was critical for conformation control and for the ease of substrate assembly, but its very existence limited this method to the synthesis of indole derivatives. While indoles are highly useful compounds, extending this chemistry to nonaromatic substrates would provide a new approach to other *N*-heterocycles.

Scheme 1. Pt-Catalyzed Formation of Tricyclic Indoles



We surmised that a *cis*-alkene could substitute the benzene ring (i.e., **1**, Scheme 2). For the ease of substrate preparation and to avoid the relatively electron-rich C−C double bond of the enamide moiety in **1**, enynyl lactam **2** with an allyl amine moiety was chosen. We expected that upon Au/Pt

(1) For selected recent reviews on Au catalysis, see: (a) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (d) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (f) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (g) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (h) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.

(2) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346–349.

(3) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546–10547.

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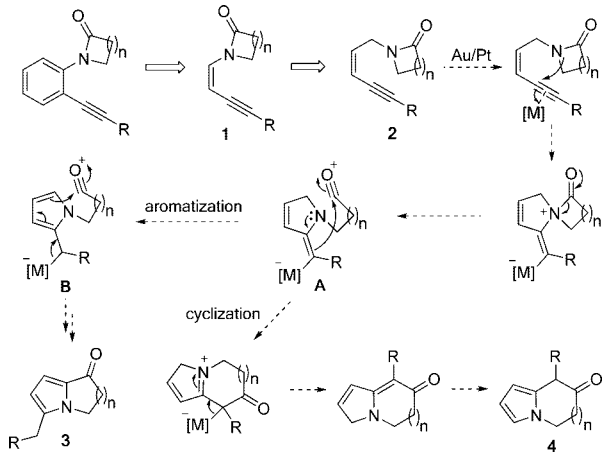
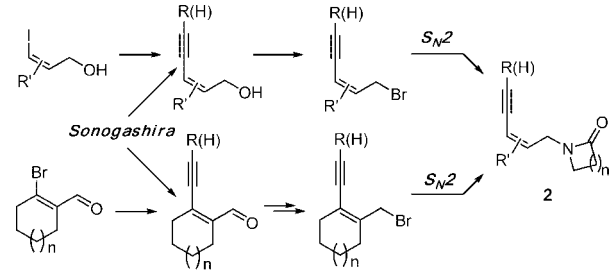
Scheme 2. Extending the Lactam Chemistry: Design



Scheme 3. General Approach for Substrate Synthesis

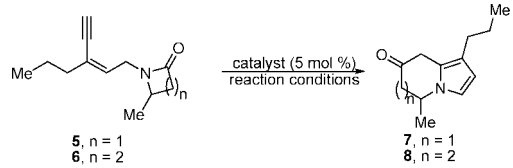


activation compound **2** would undergo a *5-exo-dig* cyclization preferentially instead of the 5-*endo-dig* cyclization observed in our previous study.[2] Nevertheless, subsequent heterolytic fragmentation of the amide bond would generate intermediate **A** possessing a highly nucleophilic acyl cation, which might undergo formal 1,5-hydride migration and thus form pyrrole acyl cation **B**. Cyclization of **B** would lead to bicyclic pyrrole **3**. Alternatively, cyclization of the acyl cation in **A** to the enamine moiety directly would afford isomeric bicyclic pyrrole **4** with a larger fused ring.

Lactam starting material **2** can be readily prepared according to two general sequences outlined in Scheme 3: from *cis*-3-iodoprop-2-en-1-ol, the C−C triple bond can be installed via the Sonogashira reaction, and the lactam moiety can be attached via an S_N2 reaction with the corresponding allylic bromide; or, for substrates with a ring-fused C−C double bond, β-bromoenals, readily available from the corresponding alicyclic ketones via Vilsmeier reaction,[4] are used.

In our initial study, strained β-lactam **5** indeed underwent cycloisomerization with $PtCl_2$ as catalyst, affording dihydroindolizinone **7** (Table 1, entry 2) albeit in only 18% yield. Notably, compound **7** was not too stable on silica gel column and also prone to oxidation over extended exposure to air; consequently, it was isolated via quick flash chromatography and stored cold under nitrogen. $PtCl_4$, the catalyst used in our previous study,[2] did not catalyze this reaction (entry 1), nor did $AuCl_3$ (entry 3). Cationic Au(I) catalysts in general were better than $PtCl_2$ (entries 4−9), and the most efficient was $IPrAuNTf_2$[5] (entries 8 and 9). The reaction solvent was critical for the success of this reaction, and anhydrous THF allowed complete conversion and up to 94% isolated yield with 10 mol % of the catalyst (entry 9). As a control experiment, $HNTf_2$ (1 equiv, entry 10) did not promote this reaction, and β-lactam **5** was completely decomposed in 15 min. In these studies, no dihydropyrrolizinone **3** was observed, suggesting that the aromatization to form **B** is relatively slow. Under the optimized reaction conditions,

Table 1. Initial Study and Reaction Conditions Optimization



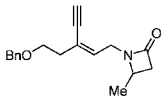
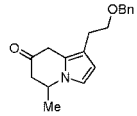
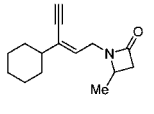
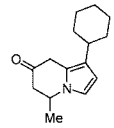
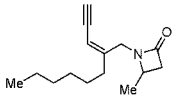
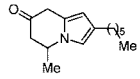
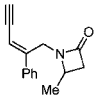
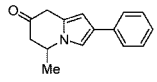
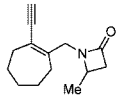
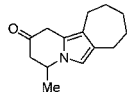
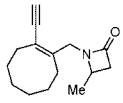
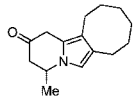
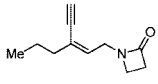
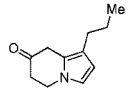
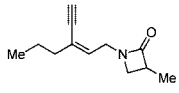
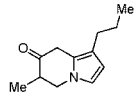
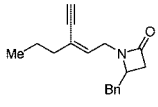
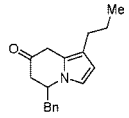
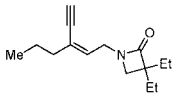
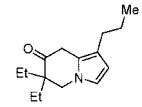
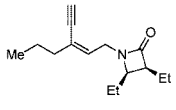
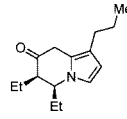
entry	substrate[a]	catalyst	reaction conditions	time	yield (%)[b]	convn (%)
1	**5**	$PtCl_4$	DCE, reflux, O_2 (1 atm)	6 h	0	*c*
2	**5**	$PtCl_2$	toluene, 80 °C, CO (1 atm)	8 h	18	70
3	**5**	$AuCl_3$	DCE, 80 °C	5 min[d]	0	*c*
4	**5**	$Ph_3PAuSbF_6$	acetone, rt	3 h	7	35
5	**5**	$Ph_3PAuNTf_2$	acetone, 45 °C	15 h	31	100
6	**5**	$Ph_3PAuNTf_2$	DCM, reflux	15 h	16	30
7	**5**	$Ph_3PAuNTf_2$	THF, 45 °C	2 h	73	100
8	**5**	$IPrAuNTf_2$	THF, 45 °C	2 h	78	100
9	**5**	$IPrAuNTf_2$[e]	THF, 45 °C	2 h	98[f]	100
10	**5**	$HNTf_2$[g]	THF, 45 °C	15 min	0	*h*
11	**6**	$IPrAuNTf_2$	THF, 45 °C	2 h	0	*c*

[a] Substrate concentration is 0.05 M. [b] Estimated by ^1H NMR using diethyl phthalate as internal reference. [c] Mostly starting material. [d] Au precipitates observed. [e] 10 mol % of the catalyst. [f] 94% isolated yield. [g] 1 equiv of $HNTf_2$. [h] The starting material was completely decomposed.

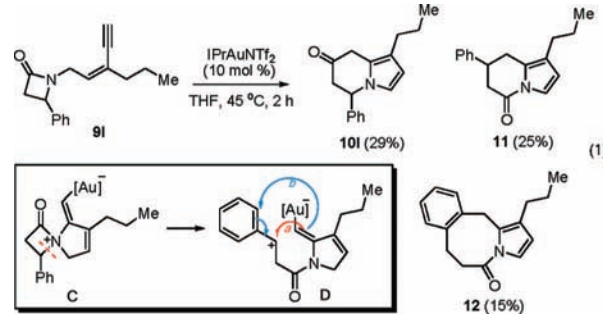
however, γ-lactam **6** remained mostly unreacted, and bicyclic pyrrole **8** was not formed, indicating the importance of the lactam ring strain for the success of this reaction.

A scope study of this chemistry was performed, and the results are shown in Table 2. While substrates with substituents at the alkyne terminus (e.g., Bu or Ph) did not undergo this catalytic reaction, various substituents at the C−C double bond were tolerated, including benzoxyethyl (entry 1) and sterically demanding cyclohexyl (entry 2) germinal to the ethynyl group and hexyl (entry 3) and phenyl (entry 4) groups vicinal to the lactam, leading to dihydroindolizinones with different substitutions at their 1- and 2-positions. Substrates with the C−C double bond embedded in medium-sized rings (entries 5 and 6) also reacted well, yielding interesting seven-/eight-membered ring fused dihydroindolizinones (e.g., **10e** and **10f**) in good yields. Surprisingly, the corresponding cyclopentene or cyclohexene substrates did not afford the corresponding five-/six-membered ring-fused dihydroindolizinones, and the starting materials were mostly unreacted for the former and partly decomposed for the later after 10 h.

Table 2. Reaction Scope for the Formation of Dihydroindolizinones[a]

entry	substrate 9[b]		product 10[c]		time	yield[d]
1		**9a**		**10a**	5 min	74%[e]
2		**9b**		**10b**	24 h	68%[e]
3		**9c**		**10c**	1 h	88%
4		**9d**		**10d**	5 min	90%[f]
5		**9e**		**10e**	4.5 h	70%
6		**9f**		**10f**	3 h	70%
7		**9g**		**10g**	5 min	90%
8		**9h**		**10h**	5 h	67%
9		**9i**		**10i**	2 h	66%[e]
10		**9j**		**10j**	12 h	69%
11		**9k**		**10k**	9 h	66%[g,h]

[a] Reaction conditions: $IPrAuNTf_2$ (5 mol %), THF (0.05 M), 45 °C. [b] The β-lactams were best used right after preparation as most of them decomposed over time. [c] Most of the products were prone to decompose under acidic conditions and over extended exposure to air. [d] Isolated yield. [e] 10 mol % of $IPrAuNTf_2$ was used. [f] 87% NMR yield was observed using a higher substrate concentration (0.1 M). [g] Reaction temperature: 55 °C. [h] The other diatereomer was not observed.



The β-lactam moiety was also studied for its substitution scope. Besides β-methyl, no substitution (entry 7), α-methyl (entry 8), β-benzyl (entry 9), α,α-diethyl (entry 10), and α,β-diethyl (entry 11) were all allowed, affording products with various substituents at the dihydroindolizinone 5- and 6-positions in acceptable yields. Of note, no *trans*-isomer of **10k** was observed, indicating little or no epimerization at the carbonyl α-position during the reaction.

When substrate **9l** with a phenyl α to the lactam nitrogen was studied, three compounds were isolated and characterized (eq 1). Besides the expected dihydroindolizinone **10l**, isomeric cyclic *N*-acylpyrrole **11** was isolated in 25% yield along with benzene-fused tricyclic pyrrole **12** (15%). This result offers support to the reaction mechanism envisioned in the initial design (Scheme 2): upon the lactam cyclization,[6] ammonium intermediate **C** could undergo amide bond heterolytic fragmentation, generating an acyl cation and eventually affording **10l**; alternatively, the fragmentation of

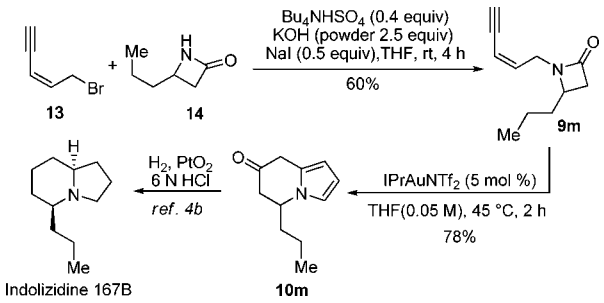
(4) (a) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541–3557. (b) Ruck-Braun, K.; Moller, C. *Chem. Eur. J.* **1999**, *5*, 1038–1044.

(5) 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidenegold(I) bis(trifluoromethanesulfonyl)imide; for its first catalysis study, see: Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159. For its synthesis, see: Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.

(6) For related studies, see: (a) Hashmi, A. S. K.; Buehrle, M.; Salathe, R.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 2059–2064. (b) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184. (c) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881–1884.

(7) For selected previous total synthesis, see: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688–4693. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513–3518. (c) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194. (d) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445–1446. (e) Guazzelli, G.; Lazzaroni, R.; Settambolo, R. *Synthesis* **2005**, 3119–3123. (f) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300–9301. (g) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409–1412.

Scheme 4. Formal Total Synthesis of Indolizidine 167B



the C(sp^3)−N bond is competitive as a result of the formation of a stable benzylic cation in **D**. Cyclization of **D** would eventually yield **11** via approach a and **12** via approach b.

This method offers an expedient and novel approach to the synthesis of indolizidine alkaloids. For example, a three-step formal synthesis[7] of indolizidine 167B, an alkaloid of scarce quantitiy isolated from neotropical poison dart frogs,[8] can be readily achieved from 5-bromo-pent-3-en-1-yne (i.e., **13**,[9] Scheme 4). Thus, a S_N2 reaction between **13** and commerically available β-lactam **14** afforded lactam **9m** in 60% yield. Subjection of **9m** to the standard Au catalysis conditions yielded dihydroindolizinone **10m** in 78% yield, which was previously converted to indolizidine 167B via hydrogenation.[7b]

In summary, we have developed an efficient Au-catalyzed method for the synthesis of 5,6-dihydro-8*H*-indolizin-7-ones from readily available enynyl β-lactam. This method allows an expedient formal synthesis of indolizidine 167B.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802159V

(8) (a) Daly, J. W. In *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: Vienna, 1982; Vol. 41, pp 205−340. (b) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectiues*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, pp 1−274.

(9) This bromide was prepared from the corresponding alcohol in 55% yield using Ph_3P/Br_2.