Advanced Synthesis & Catalysis

Accepted Article

Title: Synthesis of Eight-Membered Nitrogen Heterocycles via a Heterogeneous PtI2-Catalyzed Cascade Cycloaddition Reaction of -Aminoalkynes with Electron-Deficient Alkynes

Authors: Lingyan Liu, Xinhong Li, Songmeng Wang, Hongkai Wang, Weilin Wang, Weixing Chang, and li jing

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901644

Link to VoR: http://dx.doi.org/10.1002/adsc.201901644

10.1002/adsc.201901644

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Synthesis of Eight-Membered Nitrogen Heterocycles via a Heterogeneous PtI_2-Catalyzed Cascade Cycloaddition Reaction of δ-Aminoalkynes with Electron-Deficient Alkynes

Xinhong Li,[a] Songmeng Wang,[a] Hongkai Wang,[a] Weilin Wang,[a] Lingyan Liu, [a]* Weixing Chang,[a] Jing Li[a,b]*

[a] the State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai Uiversity, Tianjin 300071, P. R. China.
Phone: 022-23501410
E-mail: liulingyan@nankai.edu.cn; lijing@nankai.edu.cn.
[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Weijin Road 94#, Nankai District, Tianjin 300071, P. R. China

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A novel heterogeneous PtI_2-catalyzed cascade reaction of δ-aminoalkynes was developed for the synthesis of various eight-membered nitrogen heterocycles in excellent yields. The reaction proceeds via a hydration of δ-aminoalkynes and subsequent intramolecular cyclization and intermolecular addition as well as ring-expansion cascade reaction with another electron-deficient alkynes. This method has the advantages of simple operation and mild reaction conditions. And the simple PtI_2 with no any supports could be readily recycled through simple centrifugation without substantial loss of activity in 1,2-dichloroethane (DCE). The recyclability of PtI_2 may be ascribed to its insolubility in DCE. The reaction constitutes a *formal* [6+2]-cycloaddition.

Keywords: Eight-membered nitrogen heterocycles; Cascade cyclization reaction; Heterogeneous PtI_2-catalyzed; δ-aminoalkynes; hydration

Introduction

Medium-sized rings heterocyclic compounds are ubiquitous building blocks in natural products and pharmaceuticals, and eight-membered nitrogen heterocycles have been found to exhibit unique biological activities (Figure 1).[1] Organic synthesis chemists have paid more attention to develop effective methodologies for the construction of eight-membered nitrogen heterocycles in recent decade, despite their intrinsically unfavorable entropic and enthalpic factors.[2] Among them, transition metal catalyzed cycloadditions are the most attractive methods to construct medium-sized ring systems.[3] For example, Rovis's group described a rhodium-catalyzed asymmetric [4+2+2] cycloaddition of dienyl isocyanates and terminal alkynes to afford bicyclo[6.3.0] azocine derivatives (Scheme 1, eq.1).[3a] Louie and co-workers reported a Ni/P(*p*-tol)$_3$ catalyzed intermolecular cycloaddition between 1,3-dienes and 3-azetidinones/3-oxetanones to construct the eight-membered nitrogen heterocycles (Scheme 1, eq.2).[3b] Ma et. al developed [Cp*$RhCl_2$]$_2$-catalyzed [4+2+2]-cyclization between *N*-pivaloyloxy benzamides and 1,6-allene-enes to form the eight-membered lactams (Scheme 1, eq.3).[3c] Nevertheless, these methods somehow have some deficiencies, such as unsatisfactory yields, long reaction time and the limited substrates scope. Moreover, direct end-to-end cyclization to make eight-membered ring are often low yielding and the ring expansion strategy has been shown to overcome this problem[4], although the metal catalysts used are generally unrecyclable. Therefore, it is still desirable to explore a simple, mild, and efficient synthetic method for the construction of eight-membered nitrogen heterocycles in chemical and drug development.

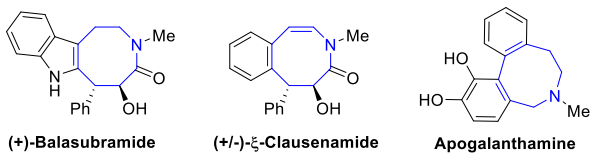
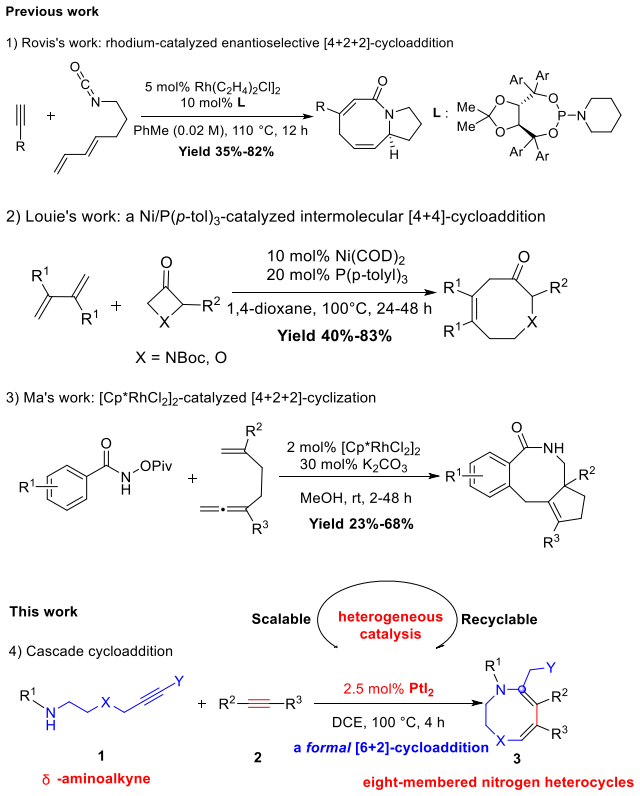


Figure 1. Biologically active natural products containing azocine skeletons.

As a continuous work on the homopropargylic amines (β-aminoalkynes) of our research group,[5] we herein developed a heterogeneous PtI_2-catalyzed cascade cycloaddition reaction of δ-aminoalkynes and electron-deficient alkynes without the need of

10.1002/adsc.201901644

additional supports (Scheme 1, eq.4). To the best of our knowledge, it is unprecedent that this simple platinum halides are used as heterogeneous catalysts in such reactions. Previous simple transition metal catalyzed reactions are most homogeneous reaction, whereas for the heterogeneous reactions, the supported metal catalysts are usually involved, such as carbon, silica gel, Al_2O_3, Fe_2O_3, molecular sieves, or polymer supports.[6] Moreover, as shown in the literature [7], this rare strategy of synthesizing 8-membered ring via a cascade reaction, involving cyclisation of a linear molecule and *in situ* ring expansion of 6-*b*-4 fused rings to 8-membered rings, has many advantages over the traditional direct end-to-end cyclization, such as offering excellent yields,.

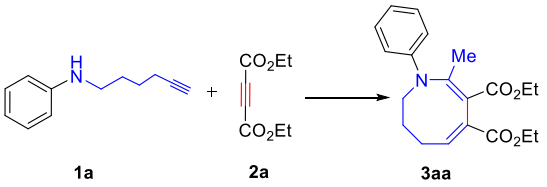


Scheme 1. The constuction of eight-membered nitrogen heterocycles.

Results and Discussion

In our initial study, we carried out some screening experiments on the reaction of δ-aminoalkyne **1a** with 2 equiv. of diethyl but-2-ynedioate (**2a**) in *N*, *N*-dimethylformamide (DMF) (Table 1). When CuOTf or AgOAc was used as a catalyst, the reaction gave the tetrahydroazocine **3aa** in low yield at 80 °C for 4 h (entries 1 and 2). Switching to use PtI_2 and Ph_3PAuCl increased the yields of **3aa** to 68% and 73%, respectively (entries 3 and 4). Gold(I) catalysts with various phosphine ligands—(2,4-di-*t*-BuPhO)$_3$P, (4-CF_3Ph)$_3$P, BINAP, and Johnphos—were further investigated and no obvious improved yield was observed even when the reaction temperature was increased to 120 °C (entries 5-8). Neither decreasing the amount of Ph_3PAuCl to 2.5 mol% nor employing $Ph_3PAuNTf_2$ as a catalyst enhanced the yield (entries 9 and 10). Examination of other solvents revealed that 1,2-dichloroethane (DCE) gave the best yield at 100 °C (entries 11–13). Intrigued by this result, we retested the catalyst previously screened ($Ph_3PAuNTf_2$, CuOTf, AgOAc, and PtI_2) in DCE at 100 °C (entries 14-17) and were surprised to find that a 99% yield of **3aa** could be obtained in the reaction of **1a** and **2a** in DCE in the presence of 10 mol% PtI_2. Moreover, the yield was maintained even when the amounts of PtI_2 and diethyl but-2-ynedioate **2a** were decreased to 2.5 mol% and 1.1 equiv., respectively (entries 18 and 19). In summary, these experiments revealed that the optimal conditions involved the use of 2.5 mol% PtI_2 and 1.1 equiv. of **2a** in DCE (0.1 M) at 100 °C.

Table 1. Optimization of conditions for the formation of eight-membered nitrogen heterocycle **3aa**[a)]



Entry	Catalyst (mol%)	Solvent	T (°C)	t (h)	Yield[b)]
1	CuOTf (20)	DMF	80	4	30
2	AgOAc (20)	DMF	80	4	30
3	PtI_2 (10)	DMF	80	4	68
4	Ph_3PAuCl (5)	DMF	80	2	73
5	(2,4-di-*t*-Bu$C_6H_3O)_3$P AuCl (5)	DMF	80	3	59[c)]
6	(4-CF_3Ph)$_3$PAuCl (5)	DMF	120	3	53[c)]
7	BINAP$(AuCl)_2$ (5)	DMF	120	3	59[c)]
8	JohnphosAuCl (5)	DMF	120	3	70[c)]
9	Ph_3PAuCl (2.5)	DMF	80	2	76
10	$Ph_3PAuNTf_2$ (2.5)	DMF	80	4	80[c)]
11	Ph_3PAuCl (2.5)	PhMe	100	4	92[c)] (88)
12	Ph_3PAuCl (2.5)	dioxane	100	4	78[c)]
13	Ph_3PAuCl (2.5)	DCE	100	4	94[c)] (88)
14	$Ph_3PAuNTf_2$ (2.5)	DCE	100	4	95[c)] (94)
15	CuOTf (20)	DCE	100	4	65[c)]
16	AgOAc (20)	DCE	100	4	65[c)]
17	PtI_2 (10)	DCE	100	4	99
18	PtI_2 (5)[d)]	DCE	100	4	99
19	PtI_2 (2.5)[d)]	DCE	100	4	99

[a)] Standard procedure: A Schlenk tube was charged with catalyst, δ-aminoalkyne **1a** (17.3 mg, 0.1 mmol), solvent (1.0 mL), and diethyl but-2-ynedioate (**2a**) (0.2 mmol, 32 μL, 2.0 equiv.) in that order, and the mixture was stirred under the specified reaction conditions and monitored by thin-layer chromatography. Abbreviations: DMF = *N*, *N*-dimethylformamide, BINAP = (+/−)-2,2'-bis(diphenyl- phosphino)-1,1'-binaphthy, Johnphos = 2-(di-*t*-butylphosphino) biphenyl, DCE = 1,2-dicloroethane. [b)] Isolated yields are provided, unless otherwise stated. [c)] The yields were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxylbenzene as an internal standard. [d)] The amount of **2a** was 1.1 equiv..

In the above described experiments, we observed that the PtI_2, a black powder, was insoluble in DCE for the duration of the process (Figure 2).

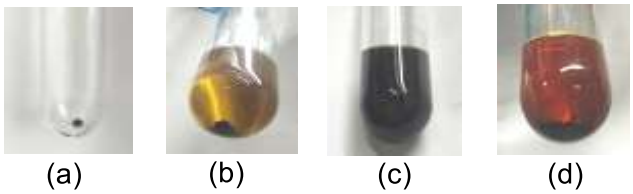
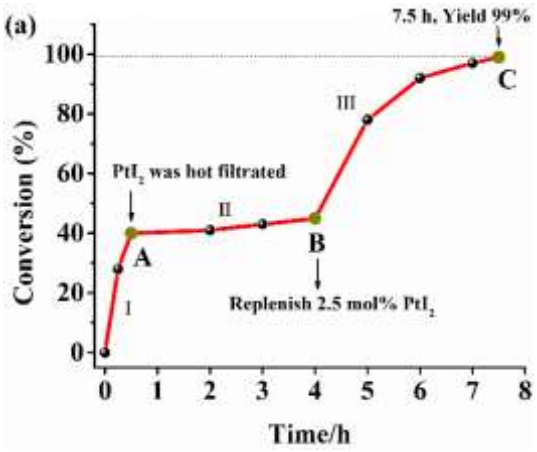
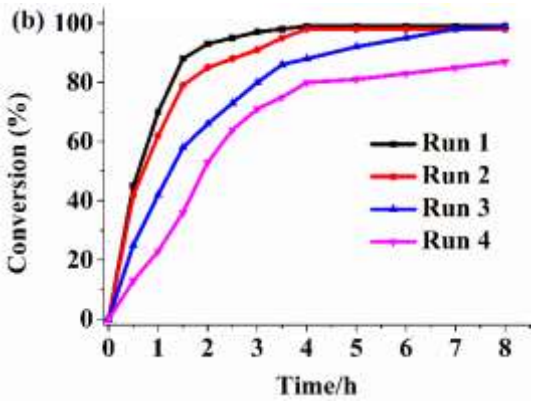


Figure 2. Picture of solubility of catalyst. (a) PtI_2 (6.7 mg, 2.5 mol%) was added initially to a Schlenk tube. (b) **1a** (103.8 mg, 0.6 mmol), **2a** (106 μL, 0.66 mmol, 1.1 equiv.), and DCE (6 mL) were subsequently added into the tube. (c) The reaction mixture was heated at 100 °C for 1 h. (d) The reaction mixture was standed for 6 h after reaction completion.

To determine whether the PtI_2 catalyst was in fact recyclable, we conducted the hot-filtration experiments.[8] In detail, after completion of the reaction, the mixture was hot-filtered through a small kieselguhr column, and the filtrate was then analyzed by inductively coupled plasma optical emission spectrometry. The analyzed results showed that the PtI_2 content in the filtrate was less than 0.2% (<2.3 μg), indicating that catalyst was almost recoverable. In addition, we conducted several other experiments to confirm the significance and reusability of the catalyst. In the presence of 2.5 mol% PtI_2, **1a** was allowed to react with **2a** in DCE at 100 °C for 30 min (Figure 3a-I, point A, 40% conversion); then the reaction mixture was rapidly hot-filtered, and the filtrate was reheated to 100 °C and maintained at that temperature for an additional 3.5 h. During this period (Figure 3a-II, point B), no additional conversion was detected. However, if another 2.5 mol% PtI_2 was added to the reaction mixture, the conversion of reation began to increase again, and a 99% yield of the product was obtained after an another 3.5 h at 100 °C (Figure 3a-III, point C).





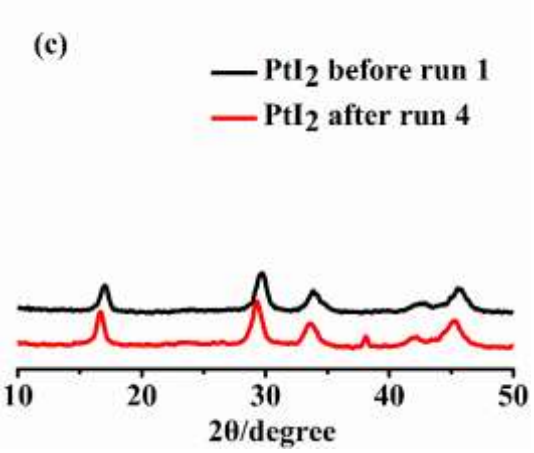


Figure 3. (a) Hot-filtration experiments. All yields were determined by ^{1}H NMR spectroscopy of the crude products with 1,3,5-trimethoxylbenzene as an internal standard. Phase I: 2.5 mol% PtI_2, 0.5 h; phase II: no PtI_2 (hot filtered), 3.5 h; phase III: 2.5 mol% PtI_2, 3.5 h. (b) Assessment of catalyst stability under batch conditions: δ aminoalkyne **1a** (34.6 mg, 0.2 mmol) was allowed to react with diethyl but-2-ynediote (**2a**, 35 mL, 0.22 mmol) in DCE (2 mL) at 100 °C for 8 h in the presence of 2.5 mol% PtI_2 (2.2 mg, 0.005 mmol). Between runs, the PtI_2 was separated by centrifugation, and then used in the next run (runs 1–4). (c) Comparison of powder X-ray diffraction patterns of PtI_2 before run 1 and after run 4.

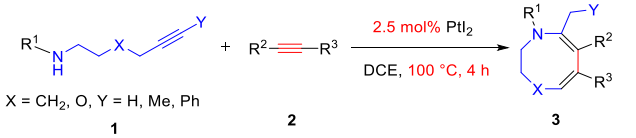
We also evaluated the stability of the catalyst.[9] In a reaction of δ-aminoalkyne **1a** (0.2 mmol) and diethyl but-2-ynedioate (**2a**, 0.22 mmol) catalyzed by 2.5 mol% PtI_2 (2.2 mg), the catalyst could be recovered by simple centrifugation and reused three times with only a small decrease in the yield of **3aa** (Figure 3b, runs 1–4). Under these kinetically controlled conditions, the changes in the apparent rate constant in the consecutive runs reflect the extent of catalyst deactivation. The catalyst stability was confirmed by comparison of its powder X-ray diffraction patterns before run 1 and after run 4 (Figure 3c). Summarily, the PtI_2 was considered as a recyclable catalyst in this reaction, as mainly ascribed to the poor solubility of the catalyst PtI_2 in DCE.

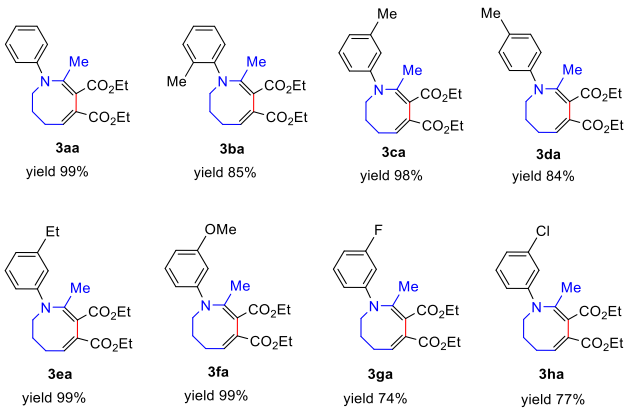
Using the optimized reaction conditions (Table 1, entry 19), we evaluated a series of δ-aminoalkynes **1** and electron-deficient alkynes **2** (Table 2). Various

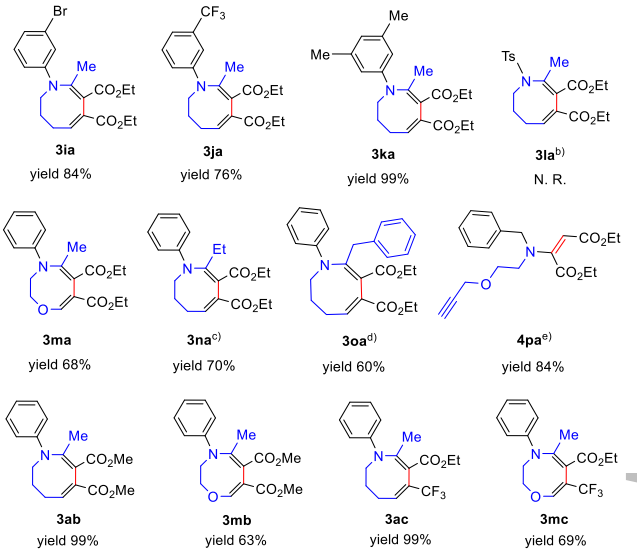
10.1002/adsc.201901644

N-aryl-substituted δ-aminoalkynes **1** were suitable substrates for reactions with **2a**, delivering the corresponding eight-membered nitrogen heterocycles (**3aa**–**3ka**) in 76–99% yields. Moreover, substrates bearing with electron-donating substituents (**3ba**–**3fa**) on the *N*-aryl ring generally gave higher yields than those with electron-withdrawing substituents (**3ga**–**3ja**). Unfortunately, *N*-tosyl aminoalkyne **1l** failed to react with **2a** even at 150 °C for 8 h. This phenomenon may be explained that the strong electron-withdrawing ability of *N*-Ts protecting group reduced the nucleophilicity of nitrogen atom, and then inhibited the intermolecular nucleophilic addition cyclization. Interestingly, δ-aminoalkyne **1m** (X = O) afforded a 68% yield of **3ma**. Moreover, reaction of an internal aminoalkyne with a methyl (**1n**) or phenyl group (**1o**) could also produce **3na** and **3oa** in good yields. In contrast, *N*-benzyl-substituted aminoalkyne **1p** gave only acyclic product **4pa**, which did not further undergo intramolecular enyne-cyclization even at increased temperature. We surmised that the electron-riched nitrogen attached to benzyl group of **1p** preferred to undergo the intermolecular nucleophilic addition with electron-deficient alkyne **2a**, instead of forming the enamine intermediate via hydration of **1p**. When dimethyl but-2-ynedioate (**2b**) was used as the alkyne, tetrahydroazocine **3ab** and oxa-tetrahydroazocine **3mb** were obtained in 99% and 63% yields, respectively. Notably, unsymmetrical electron-deficient alkyne **2c** was also a good substrate, giving regioselective **3ac** and **3mc** in 99% and 69% yields, respectively. And the regioselectivity of the reaction can be attributed to stronger electron-withdrawing ability of trifluoromethyl group than that of ester group (CO_2Et). The absolute configurations of **3aa** and **3mc** were unambiguously confirmed by X-ray single-crystal diffraction analysis (Figures S1 and S2).[10]

Table 2. PtI_2-catalyzed cascade reactions of δ-amino alkynes **1** and electron-deficient alkynes **2**.[a)]

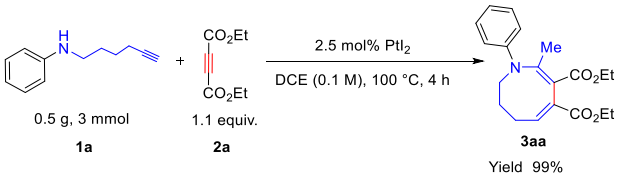






a) Standard procedure: A Schlenk tube was charged with PtI_2 (1.1 mg, 0.0025 mmol, 2.5 mol%), δ-aminoalkyne **1** (0.1 mmol), DCE (1.0 mL), and alkynyl ester **2** (0.11 mmol, 1.1 equiv.) in that order, and the mixture was stirred at 100 °C for 4 h under argon and monitored by TLC. Isolated yields are given. N.R. = no reaction. b) The reaction mixture was stirred at 150 °C for 8 h. c) The reaction was conducted at 120 °C for 5 h in the presence of PtI_2 (2.3 mg, 0.005 mmol, 5 mol%). d) The reaction was conducted step-by-step. A Schlenk tube was charged with PtI_2 (2.3 mg, 0.005 mmol, 5 mol%), δ-aminoalkyne **1o** (0.1 mmol) and DCE (1.0 mL), the mixture was stirred at 100 °C for 24 h under argon, then alkynyl ester **2a** (0.11 mmol, 1.1 equiv.) was injected to the mixture for another 4 h at 100 °C. e) The reaction was conducted at room temperature for 1 h.

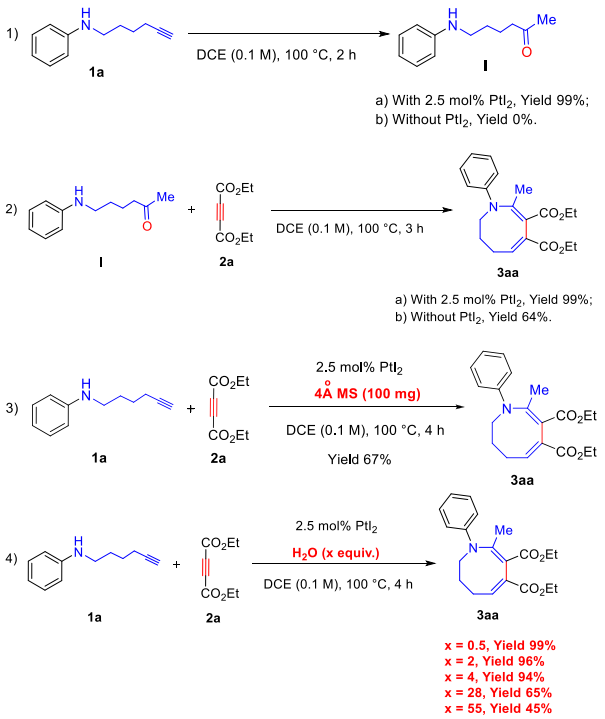
A gram-scale reaction of **1a** (3 mmol) and **2a** (3.3 mmol) produced **3aa** in 99% yield in the presence of PtI_2 (2.5 mol%) at 100 °C for 4 h in DCE (Scheme 2).

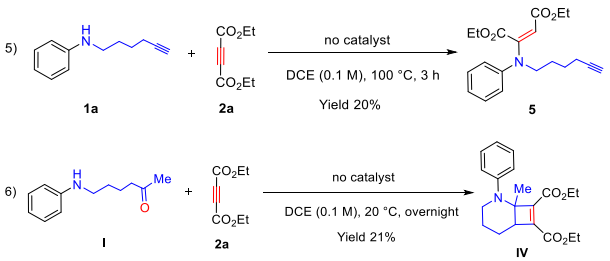


Scheme 2. Gram-scale reaction.

To gain insight into the mechanism of this cascade reaction, we conducted several control experiments. First, we found that subjecting δ-aminoalkyne **1a** to the standard conditions in the absence of alkyne **2a** gave hydration product **I** in 99% yield, whereas no reaction occurred in the absence of PtI_2 catalyst (Scheme 3, eq.1). Isolation of aminoketone **I** and subsequent reaction with diethyl but-2-ynedioate (**2a**) delivered a 99% and 64% yields of tetrahydroazocine **3aa** in the presence or absence of PtI_2 for the same reaction time (Scheme 3, eq.2). These results demonstrated that the PtI_2 was requisite to the hydration of δ-aminoalkyne **1a**. To confirm that the

hydration product was involved in the reaction, we added either 4Å molecular sieves or water (0.5 to 55 equiv) to the reaction mixture and found that the yield of **3aa** was lower in the presence of 4Å molecular sieve (Scheme 3, eq.3), and a small amount of water added had no obvious deleterious effect on the reaction outcome, while a large amount of water would complicate the reaction system and significantly reduce the yield of product (Scheme 3, eq.4). Taken together, we surmised that a trace amount of water in the system was conducive to the reaction. And the source of water may come from the materials and DCE solvent as well as during the course of feeding in the air. Moreover, the determination of moisture content has been done by titration experiments, the results showed that the total water content was 100 ppm (about 0.1 mg H_2O) for the reaction system (0.1 mmol **1a** and 1 mL DCE), it may not enough to achieve completely hydration of the alkynes. Nevertheless, the aminoketone was then transformed to the cycloenamine with the elimination of one molecular H_2O. In other words, the whole reaction needs only trace amount of water to undergo the hydration of alkyne concomitant with the formation of high reactive cycloenamine and subsequent transformation. Additionally, in the absence of PtI_2 catalyst, the reaction of **1a** and **2a** afford a intermolecular hydroamination product **5** in 20% yield with most substrate remained and with no **3aa** produced (Scheme 3, eq.5). This result further indicates that PtI_2 mainly accelerates the hydration of aminoalkyne and the formation of enamine intermediate, has no significant promotion of subsequent intermolecular nucleophilic addition reaction.[11] Fortunately, the reaction of aminoketone **I** with **2a** was conducted at 20 °C to afford the intermediate **IV**, which was isolated by column chromatography (neutral alumina), and the sructure was confirmed by NMR spectra.[12]





Scheme 3. Controlled experiments.

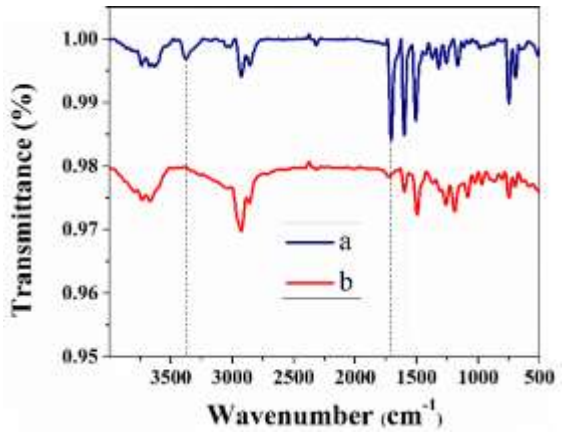
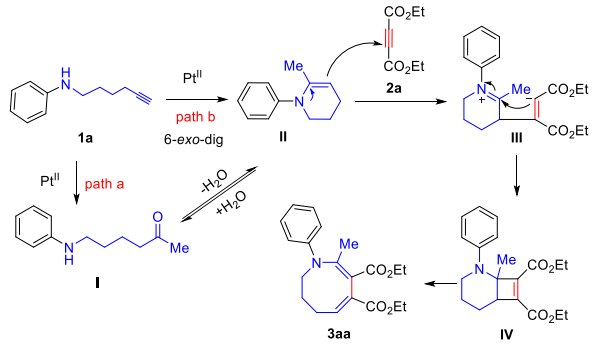


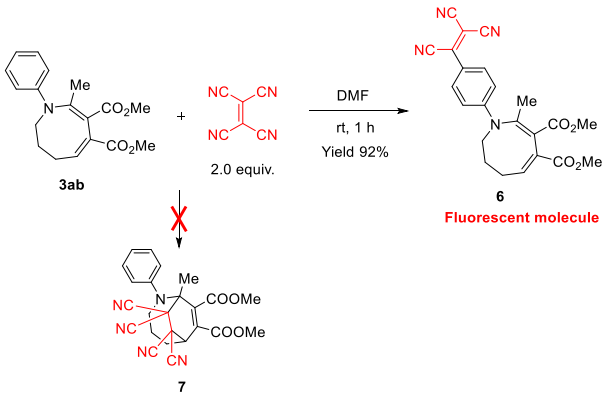
Figure 4. IR spectrum of aminoketone **I** in toluene: (a) Without molecular sieve. (b) With 5 Å molecular sieve after 12 h at 120 °C.

Besides, we added 5Å molecular sieve to the aminoketone **I** in toluene, found that both the NH stretching vibration (3381 cm^{-1}) and the carbonyl stretching vibration (1706 cm^{-1}) of aminoketone **I** nearly disappeared in IR spectroscopy, as well as with the appearance of new weak enamine deformation vibration (1599 cm^{-1}). It was inferred that cycloenamine intermediate **II** was generated (Figure 4).[13]

On the basis of the above all experiments, we proposed a possible mechanism shown in Scheme 4. In the presence of PtI_2, δ-aminoalkyne **1a** is hydrated to generate aminoketone intermediate **I** (path a), which is subsequently transformed to enamine intermediate **II** via intramolecular cyclocondensation and deprotonation reactions. The Intermediate **II** undergoes an intermolecular nucleophilic addition reaction with electron-deficient alkyne **2a** to generate intermediate **III**, and a concomitant intramolecular cyclization reaction gives fused cyclobutene intermediate **IV**. This intermediate is readily converted to eight-membered nitrogen heterocycle **3aa** via ring expansion,[14] owing to the highly strained skeleton and sterically bulky substituents of **IV**. It should be noted that the direct intramolecular 6-*exo*-dig hydroamination cyclization of **1a** to give intermediate **II** (path b) cannot be ruled out.



Scheme 4. Possible reaction mechanism.



Scheme 5. Transformation of tetrahydroazocine **3ab**.

Finally, we disclosed that reaction of tetrahydroazocine **3ab** with commercially available tetracyanoethene yielded tricyanovinylated aniline derivative **6** rather than expected [4+2]-cycloadduct **7** (Scheme 5). Interesting, **6** possessed fluorescent properties,[15] displaying different colors in various polar solvents in daylight (Figure S4). The absorption and emission spectra of **6** were measured in these solvents (Figures S5 and S6, Tables S1 and S2), and the results indicated that the absorption wavelength of **6** increased with increasing solvent polarity; specifically, the absorption maxima was red-shifted from 480 in *n*-hexane to 517 nm in dimethylsulfoxide (DMSO) (Figure S5).

Conclusion

A recyclable platinum-catalyzed cascade reactions of δ-aminoalkynes and electron-deficient alkynes was developed for the synthesis of tetrahydroazocines. The recyclability of PtI_2 catalyst was supported by several experiments and confirmed by some analytical determination, and the PtI_2 catalyst could be easily recovered by simple centrifugation and reused without substantial loss of activity. This highly efficient cascade reaction affords a variety of eight-membered nitrogen heterocycles in excellent yields. And a reasonable mechanism was proposed based on some controll experiments and solid evidences, namely, hydration of the δ-aminoalkynes and subsequent intramolecular cyclization-intermolecular nucleophilic addition-intramolecular cycloaddition-ring expansion cascade sequence was involved in this reaction. This method provides a novel strategy for the construction of medium-sized ring. In addition, product **3ab** could be used as a starting material for the synthesis of fluorescent molecule **6**. Further functionalization transformation of products is on progress in our group.

Experimental Section

General Method for the Synthesis of product 3

To a dried Schlenk tube was added PtI_2 (1.2 mg, 2.5 mol%), different δ-aminoalkynes **1** (0.1 mmol), alkynylesters **2** (0.11 mmol, 1.1 equiv.) and DCE (1 mL) were sequentially added under Ar atmosphere, the mixture was stirred at 100 °C until δ-aminoalkynes **1** disappear (monitored by TLC). Then filtered, the filtrate was concentrated *in vacuo* to give the residue, which was purified by column chromatography with gradient elution (Silica gel, petroleum ether : ethyl acetate = 10 : 1) to give the final products **3**.

Acknowledgements

We are grateful for financial support from the National Key Research and Development Program of China (no. 2017YFD0201404) and the National Natural Science Foundation of China (no. 21873051), as well as from the Natural Science Foundation of Tianjin City (no. 17JCZDJC37300). We also acknowledge support from the Collaborative Innovation Center of Chemical Science and Engineering (Tianjin).

References

[1] a) M.-H. Yang, Y.-Y. Chen, L. Huang, *Phytochemistry* **1988**, *27*, 445-450; b) B. Riemer, O. Hofer, H. Greger, *Phytochemistry* **1997**, *45*, 337-341; c) Y. Ishida, K. Sadamune, S. Kobayashi, M. Kihara, *J. Pharmacobiodyn.* **1983**, *6*, 391-396.

[2] a) I. Shiina, *Chem. Rev.*, **2007**, *107*, 239-273; b) G. Illuminati, L. Mandolini, *Acc. Chem. Res.*, **1981**, *14*, 95-102; c) A. Michaut, J. Rodriguez, *Angew. Chem. Int. Ed.* **2006**, *45*, 5740-5750; d) Z. X. Yu, Y. Wang, Y. Y. Wang, *Chem. Asian J.* **2010**, *5*, 1072-1088.

[3]a) R.-T. Yu, R. K. Friedman, T. Rovis, *J. Am. Chem. Soc.*, **2009**, *131*, 13250-13251; b) A. Thakur, M. E. Facer, J. Louie, *Angew. Chem., Int. Ed.*, **2013**, *52*, 12161-12165; c) S.-Z. Wu, R. Zeng, C.-L. Fu, Y.-H. Yu, X. Zhang, S.-Q. Ma, *Chem. Sci.*, **2015**, *6*, 2275-2285; d) I. Nakamura, Y. Sato, K. Takeda, M. Terada, *Chem. Eur. J.* **2014**, *20*, 10214-10219; e) K. C. Majumdar, S. Mondal, D. Ghosh, *Tetrahedron Lett.* **2010**, *51*, 348-350.

[4] For recent papers that use ring expansion methods to improve the efficiency of nitrogen containing medium-sized rings, see: a) T. C. Stephens, W. P. Unsworth. *Synlett.* **2020**, *31*, 133-146; b) J. R. Donald, W. P.

Unsworth, *Chem. Eur. J.* **2017**, *23*, 8780–8799; c) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 2225-2230; d) T. C. Stephens, M. Lodi, A. M. Steer, Y. Lin, M. T. Gill, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 13314-1318. e) L. Li, Z.-L. Li, F.-L. Wang, Z. Guo, Y.-F. Cheng, N. Wang, X.-W. Dong, C. Fang, J.-J. Liu, C.-H. Hou, B. Tan, X.-Y. Liu, *Nat. Commun.* **2016**, *7*, 13852; f) C. Kitsiou, J. J. Hindes, P. I'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2015**, *54*, 15794-15798.

[5] For recent work on reactions of homopropargylic amines by our group, see: a) Y.-F. Kong, Y.-Z. Liu, B.-Y. Wang, S.-L. Li, L.-Y. Liu, W.-X. Chang, J. Li, *Adv. Synth. Catal.* **2018**, *360*, 1240-1252; b) L. Wang, L.-Y. Liu, W.-X. Chang, J. Li, *J. Org. Chem.* **2018**, *83*, 7799-7813; c) H.-K. Wang, C. Wang, K. M. Huang, L.-Y. Liu, W.-X. Chang, J. Li, *Org. Lett.* **2016**, *18*, 2367-2370; d) X.-H. Li, S.-M. Wang, S.-L. Li, K.-M. Li, X. Mo, L.-Y. Liu, W.-X. Chang, J. Li, *J. Org. Chem.* **2019**, *84*, 1288-1298.

[6] a) Y. Takenaka, T. Kiyosu, J. C. Choi, T. Sakakuraa, H. Yasuda, *Green Chem.* **2009**, *11*, 1385-1390; b) A. K. Shil, P. Das, *Green Chem.* **2013**, *15*, 3421-3428; c) S. M. A. H. Siddiki, K. Kon, K. Shimizu, *Green Chem.* **2015**, *17*, 173-177; d) S. M. A. H. Siddiki, K. Kon, K. Shimizu, *Chem. Eur. J.* **2013**, *19*, 14416-14419; e) Y. Preger, T. W. Root, S. S. Stahl, *ACS Omega.* **2018**, *3*, 6091-6096; f) S. P. Pitre, J, C. Scaiano, T. P. Yoon, *ACS Catal.* **2017**, *7*, 6440-6444. g) J. M. Alonso, M. P. Munoz, *Angew. Chem. Int. Ed.* **2018**, *57*, 4742-4746; h) M. A. R. Jamil, A. S. Touchy, M. N. Rashed, K. W. Ting, S. M. A. Hakim Siddiki, T. Toyao, Z. Maeno, K. Shimizu, *J. Catal.* **2019**, *371*, 47-56.

[7] A. Lawer, J. A. Rossi-Ashton, T. C. Stephens, B. J. Challis, R. G. Epton, J. M. Lynam, W. P. Unsworth, *Angew. Chem., Int. Ed.* **2019**, *58*, 13942-13947.

[8] X.-J. Yang, T. Liang, J.-X. Sun, M. J. Zaworotko, Y. Chen, P. Cheng, Z.-J. Zhang, *ACS Catal.* **2019**, *9*, 7486-7493.

[9] S. L. Scott, *ACS Catal.* **2018**, *8*, 8597-8599.

[10] Crystal data for the compound **3aa**: $C_{20}H_{25}NO_4$, MW 343.41, Monoclinic, C2/c, Final R indices [I> 2ó(I)], R1 = 0.0598, wR2 = 0.1540, R indices (all data) R1 = 0.0769, wR2 = 0.1689, a = 30.391 (6) Å, b = 8.1281 (16) Å, c = 17.670 (4) Å, V) 3684.9 (16) A^3, T) 113 K, Z) 8. Reflections collected / unique: 4399/ 3475 [R(int) = 0.046], number of observations [>2ó(I)] 4399, parameters) 246, Goodness-of-fit on F^2) 1.085. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 1834346. Crystal data for the compound **3mc**: $C_{17}H_{18}F_3NO_3$, MW 341.32, monoclinic, $P2_1/c$, Final R indices [I> 2ó(I)], R_1 = 0.0584, wR_2 = 0.1875, R indices (all data) R_1 = 0.0900, wR_2 = 0.1492, a = 8.4341 (8) Å, b = 11.5843 (17) Å, c = 16.7267 (18) Å, V) 1605.6 (3) A^3, T) 120 K, Z) 4. Reflections collected / unique: 7269/ 3706 [R(int) = 0.038], number of observations [>2ó(I)] 2491, parameters) 219, Goodness-of-fit on F^2) 0.91. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 1941876.

[11] X.-Y. Liu, C.-M. Che, *Angew. Chem. Int. Ed.* **2009**, *48*, 2367-2371.

[12] G.-Q. Xu, J.-T. Xu, Z.-T. Feng, H. Liang, Z.-Y. Wang, Y. Qin, P.-F. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 5110-5114.

[13] M. Hans, D. Heinz, *Arch. Pharm.*, **1986**, *319*, 1049-1052.

[14] a) B. Rao, J. H. Tang, Y. Wei, X. M. Zeng, *Chem. Asian J.* **2016**, *11*, 991-995; b) C. P. Michael, K. C. Virginia, V. D. Carl, *J. Am. Chem. Soc.* **1989**, *111*, 5824-5831; c) A. Thakur, M. E. Facer, J. Louie, *Angew. Chem. Int. Ed.* **2013**, *52*, 12161-12165; d) W. B. Cao, X. Q. Chu, Y. Zhou, L. Yin, X. P. Xu, S. J. Ji, *Chem. Commun.* **2017**, *53*, 6601-6604; e) W.-X. Zhao, Z.-G. Li, J.-W. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 4680-4683; f) W.-X. Zhao, H. Qian, Z.-G. Li, J.-W. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 10005-10008.

[15] a) A. K. Sanap, G. S. Shankarling, *Catal. Commun.*, **2014**, *49*, 58-62; b) T. Deligeorgiev, N. Lesev, S. Kaloyanova, *Dyes Pigments*, **2011**, *91*, 74-78.

10.1002/adsc.201901644

FULL PAPER

Synthesis of Eight-Membered Nitrogen Heterocycles via a Heterogeneous PtI_2-Catalyzed Cascade Cycloaddition Reaction of □δ-Aminoalkynes with Electron-Deficient Alkynes

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Xinhong Li,[a] Songmeng Wang,[a] Hongkai Wang,[a] Weilin Wang,[a] Lingyan Liu, [a]* Weixing Chang,[a] Jing Li[a,b]*