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FULL PAPER

Rh-Catalyzed Domino Hydroformylation Double Cyclizations of Arylacetylenecarboxamides*: Diastereoselectivity Study and Application for the synthesis of* 1-Azabicyclo[x.y.0]alkanes

Jui-Chi Tsai, Yi-Huei Lin, Guei-Tang Chen, Yu-Kai Gao, Yu-Che Tseng, Chien-Lun Kao and Wen-Hua Chiou*

Abstract: A domino method for the rapid syntheses of 1-azabicyclo[x.y.0]alkane scaffolds such as indolizidines, quinolizidines, decahydropyridoazepines, and their derivatives, has been developed. The strategy used for the construction of the alkaloid scaffolds involves Rh-catalyzed hydroformylation of allyl-, 3-butenyl-, or homoallyl amides, followed by two spontaneous ring closures under mild conditions. By changing the substituent position at amide substrates and altering the carbon chain length of the substrates, the reaction scope and the diastereoselectivity have been fully explored. This method can be applied to the syntheses of natural alkaloid tashiromine and epilupinine. The obvious difference in reactivity of two isomeric amide substrates, 3-butenamide **1j** and homoallylamide **1i**, could be attributed to a better HOMO-LUMO overlapping in the TS derived from butenamides during cyclization. The explanations have been supported by the corresponding DFT calculations.

Introduction

Recently, employment of a domino reaction design has proven to be an efficient and popular strategy to synthesize complicate structures. [1] Such a process does not only allow rapid transformations from simple starting materials to a complex molecule, but also reduces the production costs such as consumption of solvents, reagents, and energy, which become increasingly crucial issues in years. [2] The design of a domino reaction to synthesize specific sophisticated targets with considerable structural and stereochemical complexity appeals to be a significant intellectual challenge. Therefore, domino reactions have received considerable attention from the synthetic organic community. We have developed a strategy of aromatic-mediated domino hydroformylation double cyclization, and applied to synthesis of tricyclic alkaloid crispine A over three steps. [3] Therefore, based on the useful concept, we have reported an alkyne-mediated domino hydroformylation/double cyclization for preparation of indolizidine alkaloids.[4] The success encourages us to study thoroughly the scope and the limitation of the domino reaction. Hopefully, we are able to obtain a clear understanding of the methodology and apply it to syntheses of natural alkaloid products.

Indolizidine and quinolizidine alkaloid families have been widely distributed among a large number of natural products. [5] Many compounds in the family possess a wide range of important pharmacological activities. For example, epilupinine, a quinolizidine alkaloid isolated from *Lupinus leteus*, exhibits significant activity against leukaemia P-388 and L1210 leukaemia. [6] Additional pharmaceutical activities such as antiviral, antiarrhythmic and platelet anti-aggregating properties have also been reported. [7] The ring conformations of azabicyclic compounds with different ring sizes also dictate the orientation of the nitrogen lone pair in space, resulting important consequences on the activities. [8] Therefore, physiological activities of azabicyclic compounds have prompted many synthetic chemists to develop various elegant approaches. [9]

In the preliminary communication, we demonstrate the domino reaction strategy by using allylamides for readily preparation of indolizidines. In this work, we describe our whole findings as a full account, which includes the reaction scope, the limitation, the application for syntheses of natural alkaloids, and the rationale for the reactivity difference in isomeric homoallylamide and 3-butenamide in the process.

Results and Discussion

Our synthetic strategy is to take advantage of the domino reaction sequence: hydroformylation of olefin **1** to the corresponding aldehyde **2**, intramolecular condensation with the amide group to hemiaminal **3**, dehydration to transient *N*-acyliminium **4**, cyclization by the adjacent acetylene group as a π carbon nucleophile to the aromatic-stablized vinyl cation **5**. The cation **5** is best described as an ethenylidenylaryl cation species. Subsequent addition with an acetic acid to the final enolacetate **6**. Two classes of amides have been designed for investigation on the domino reaction. One is the allyl/homoallyl amides, in which the alkene part is located on the amine side and the nucleophile moiety is on the carbonyl side. Only difference between allylamides and homoallylamides is the length of the carbon chain. The substrates are readily available from couplings of the corresponding acids with either allylamines or homoallylamines. The other is the 3-butenamides, in which the nucleophile part is on the amine side and the alkene moiety is on the carboxyl side.

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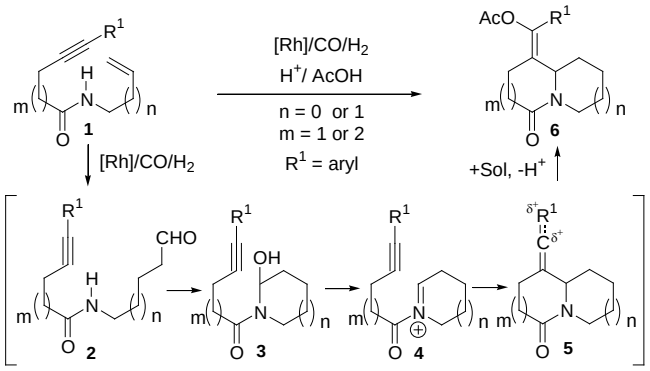
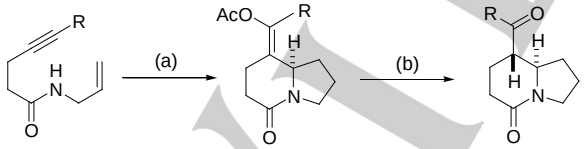
It is obvious that the ability of the nucleophile to trap the resulting *N*-acyliminium is very critical in the double cyclization (Scheme 1).



Scheme 1. The Domino hydroformylation Double Cyclization Reactions for the allyl-/homoallylamides.

Substrate Optimization: Our investigation commenced with hydroformylation on *N*-Allylamide **1a** bearing a phenylacetylene group. [10] Treatment of amide **1a** under hydroformylation conditions, [3] i.e., Rh-BIPHEPHOS [11] (0.5 mol%) and pTSA (10 mol%) at 60 ˚C under 2 atm of CO and 2 atm of H_2 in acetic acid afforded a mixture of cyclized product **6a** and unidentified side products. After purification, enolacetate **6a** was obtained in 32% isolated yield (Scheme 2). Although the yield is not satisfactory, the preliminary results demonstrate the reaction is feasible for the construction of the indolizidine skeleton. The poor yield may attribute to that the second cyclization proceeds incompletely. Hence, we anticipate that introduction of an electron donating group on the phenyl moiety should enhance the nucleophilicity of the acetylene moiety to afford the better yield. Based on the suggestion, amide **1b** bearing a *para*-methoxyphenyl group was subjected to the conditions, which give only single enolacetate **6b** in 83% isolated yield with an *E* configuration. The configuration is unambiguously determined by the ROESY spectra, which give a strong correlation between the phenyl protons (H-2') and the bridgehead proton (H-8a).

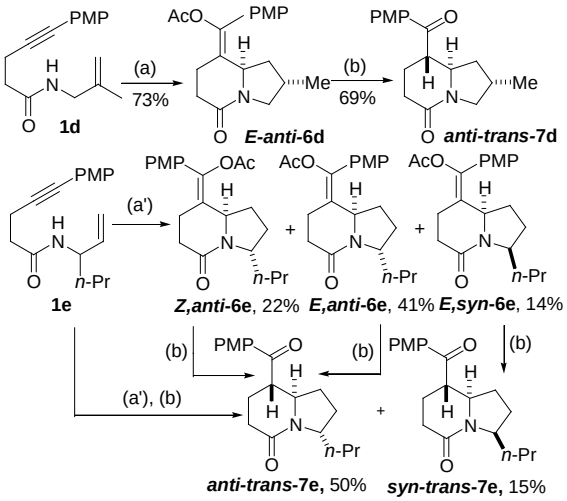


(a) Rh(acac)$(CO)_2$ (0.5 mol%); BIPHEPHOS (1.0 mol%) CO (2 atm) H_2 (2 atm) pTSA (10 mol%), AcOH, 60 ^{O}C. (b) K_2CO_3 (25 mol%) MeOH, rt.

Scheme 2. Results of three nucleophiles in the double cyclization reaction and the subsequent hydrolysis.

Exposure of *E*-enolacetate **6b** in a basic methanol solution afforded only single *trans*-ketone **7b** in 81% yield. It is noteworthy that treatment of enolacetates in acidic conditions led to formation of messy residues. A large coupling constant of 10.8 Hz was observed between the bridgehead methine and the methine next to the ketone group, i.e., H-8a and H-8, indicating a *trans* configuration between two adjacent methines. The preliminary DFT calculations on stability indicate *trans*-ketone **7b** is more stable than *cis*-ketone **7b** by 4.1 kcal/mol *in vacuo*, which suggests that the *trans* isomer is preferentially favored under thermodynamic control in the basic methanolysis of indolizidine enolacetate **6b**.

Study on the Diastereoselectivity of Substituted Allylamides: With substrates bearing the optimized carbon nucleophile, i.e., *para*-methoxyphenylacetylene, we turn our attention on how an additional substituent effects the relative stereochemistry in the product. Therefore, we designed a series of amides substrates bearing with an alkyl group at available positions for the double cyclization reactions. First of all, amide **1d**, a *gem*-disubstituted alkene bearing a methyl group at the 2 position (using the indolizidine numbering system), [12] was subjected within the pressurized double cyclized conditions, in which a higher pressure is required for hydroformylation of *gem*-disubstituted olefins. Moreover, due to a significant environmental difference of two terminus of the gem-alkene group, the use of triphenylphosphite is able to produce an excellent selectivity for the linear aldehyde. A slightly more Rh catalyst loading guarantees the complete reaction within 24 h. Gratifyingly, treatment of amide **1d** in the conditions afforded only a single *E*-*anti* product **6d** in 73% yield. Here the term of "*anti*" is used to describe the relative configuration between the C-2 position with the bridgehead methine. Subsequent basic methanolysis of *E*-*anti* enolacetate **6d** produced a single *anti*-*trans* ketone **7d** in 69% yield, showing an excellent diastereoselectivity (Scheme 3).



(a) Rh(acac)$(CO)_2$ (2 mol%); $P(OPh)_3$ (4 mol%) CO (20 atm) H_2 (20 atm) pTSA (10 mol%), AcOH, 60 ^{O}C. (a') Rh(acac)$(CO)_2$ (1 mol%); BIPHEPHOS (2 mol%) CO (2 atm) H_2 (2 atm) pTSA (10 mol%), AcOH, 60 ^{O}C.(b) K_2CO_3 (25 mol%) MeOH, rt.

Scheme 3. Results of amide **1d** and **1e** in the reactions.

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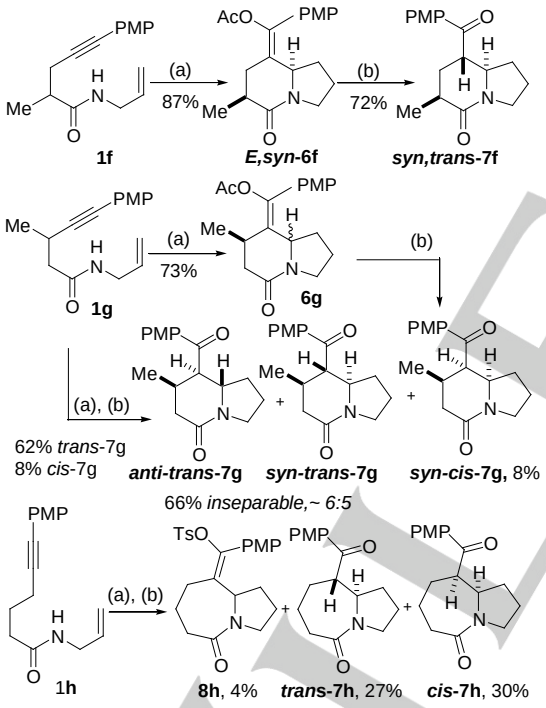
In the same manner, the reaction of **1e**, bearing an *n*-propyl group at the 3 position, affords *Z-anti* enolacetate **6e** (22%), *E-anti* enolacetate **6e** (41%), *E-syn* enolacetate **6e** (14%). While the ROESY between the phenyl protons (H-2') and the bridgehead proton (H-8a) is observed in the *E* enol-acetates, the observation of a strong ROESY correlation between the phenyl protons and the methylene group, i.e., H-7 proton, confirms the *Z* configuration. Subsequent individual methanolysis for either *Z-anti* enolacetate **6e** or *E-anti* enol acetate **6e** led to the formation of the same product, which was identified as *anti-trans* ketone **7e**. In a similar manner, methanolysis of the other *E-syn* enolacetate **6e** afforded as *syn-trans* ketone **7e**. Direct treatment of the crude reaction mixture of **1e** in the basic solution has been carried out, yielding *anti-trans* ketone **7e** (50%) and *syn-trans* ketone **7e** (15%). Thus, the results are consistent with those in the individual hydrolysis.

Different from the reaction of **1e**, reaction of amide **1f** which bears a methyl group at the 6 position, produced only single *syn* product **6f** in 87% yield. The results indicate that the 6 position was an excellent stereogenic center. Subsequent methanolysis of enolacetate **6f** at room temperature proceeded smoothly to yield single ketone *syn-trans*-**7f** in 72% yield (Scheme 4).



(a) $Rh(acac)(CO)_2$ (0.5 mol%); BIPHEPHOS (1.0 mol%) CO (2 atm) H_2 (2 atm) pTSA (10 mol%), AcOH, 60 ^{O}C. (b) K_2CO_3 (25 mol%) MeOH, rt.

Scheme 4. Results of amide **1f**, **1g** and **1h** in the reactions.

However, treatment of amide **1g**, bearing a methyl group at the 7 position, under the standard conditions gave an inseparable mixture of both *anti/syn E*-enolacetate **6g** (~ 1: 1) in 73% yield. The following methanolysis of the mixture resulted in the formation of three different ketones: an inseparable mixture of *anti-trans*-ketone **7g** and *syn-trans*-ketone **7g** in 66% isolated yield and the minor product *syn-cis*-ketone **7g** in 8% yield. A small amount of *syn-cis*-ketone **7g** has been obtained in spite of appearance of *anti-trans*-ketone **7g** and *syn-trans*-ketone **7g** as the major products. Therefore, substitution at the **7** position is quite detrimental for the diastereoselectivity in the second cyclization, and adverse to the formation of *trans* ketone in methanolysis reaction. Reaction of **1h** bearing a hex-5-ynamide moiety (m = 2) afforded enol tosylate **8h** and an inseparable mixture of *E* and *Z* enol acetate **6h** (73%, ~ 1: 1, Scheme 4). Different from the single product formation after methanolysis of the enol acetate **6b**, the methanolysis of the *E/Z* enol acetate mixture **6h** yielded two ketones, identified as *trans* ketone **7h** and *cis* ketone **7h**. Direct treatment of the crude product in the basic solution yielded *trans* ketone **7h** (27%) and *cis* ketone **7h** (30%), accompanied with enol tosylate **8h** (4%). The results also imply that *cis*-ketones **7h**, is no less stable than *trans*-ketones **7h** in the 1-azabicyclo[5.3.0] system, which is different from that *trans*-ketones is more stable in the 1-azabicyclo[4.3.0] system.

The observed selectivity for the substituted allylamides has been summarized in the figure 2. Both C-2 and C-6 Substituted allylamides reacts efficiently to provide single isomer as the product. The reaction of gem-disubstituted substrate **1d** required more pressure to give the 2,8a-*anti* product **6d**, while the reaction of allylamide **1f** proceeds at low pressure to yield the 6,8a-*syn* product **6d**. The results have shown that the C-3 position is not a good stereogenic center because of the formation of three different products in the reaction of the C-3 substituted allylamide **1e**. Although the dominated products with E- and Z- 3,8a-*anti*-enolacetate products are able to be hydrolysed to the identical ketone derivative *anti-trans* ketone **7e**, a small amount of 3,8a-*syn* product has been observed. As regards the C-7 substituted substrate **1g**, the substitution at the C-7 position has deteriorated the selectivity in the reaction. Both *syn* and *anti* enolacetate products have been formed in equal amount as an inseparable mixture. Hence, we conclude that the diastereoselectivity in the double cyclization of allylamides is excellent in substitution on the C-2 and C-6 position, mediocre in substitution on the C-3 position and poor in substitution on the C-6 position.

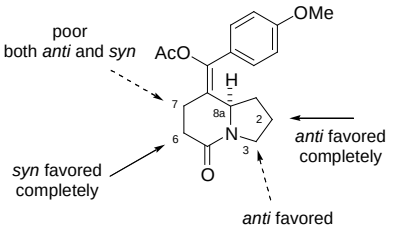


Figure 1. Summaries of the observed diastereoselectivity of various substituted allylamide substrates **1d**, **1e**, **1f**, and **1g**.

The following hydrolysis of enolacetates is also highly stereoselective in the indolizidine scaffold. In the hydrolysis of the C-2, C-6 and C-3 substituted enolacetates, all the resulting ketones possess the 8-8a-*trans* configuration, even in the cases of two diastereomeric enolacetate 3,8a-*anti and* 3,8a-*syn* enolacetate **6e**. Only small amount of *cis* ketone has been found

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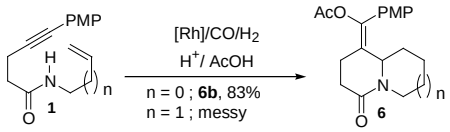
in the hydrolysis of enolacetate **6f.** The results suggest that formation of the *trans*-ketone is thermodynamically driven. However, in the 1-azabicyclo[5.3.0] system, the stability difference between the *trans* and *cis* isomer is not so significant that one of the product dominates in the reaction.

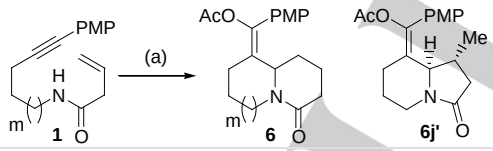
Encouraged by the successful application to indolizidines using the allylamide substrates, we prepared homoallylamide **1i**, i.e., n = 1, and wished to achieve the construction of a quinolizidine using the one-pot domino reaction strategy. However, attempts to synthesize quinolizidines directly from the reaction of the homoallylamide **1i** were unsuccessful despite intense efforts to optimize the conditions, and only resulted in a complex residue or nonspecific decomposition rather than the desired product (Scheme 5).



Scheme 5. Reaction of allylamide **1b** and homoallylamide **1i**.

Study on 3-butenamides: We therefore considered the reactivity should be related in the geometry of the corresponding TS (*vide infra*), in which poor arrangement may cause the instable TS and prevent the cyclization. Mann et al. have reported the practical demonstration of the use 3-butenamide in the hydroformylative domino reaction. [13] Therefore we turned our attention to the corresponding 3-butenamide **1j**, which was just simple swapping the carbonyl group for the methylene group next to the amide nitrogen in the homoallylamide. 3-butenamides were readily prepared from the corresponding amines with 3-butenoic acid or 2-methyl-3-butenoic acid. With 3-butenamides in hand, the substrate scope of the reaction was then explored as listed in Table 1.

Table 1. The resutls of double cyclization of 3-butenamides **1i~l.**.

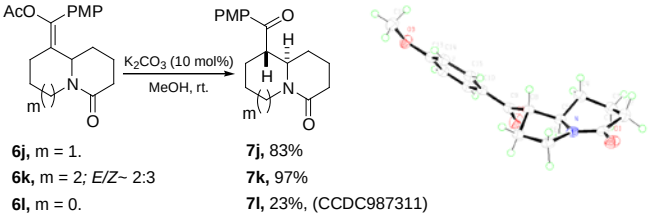


Entry[a]	Substrate	P_{CO} (atm)	P_{H2} (atm)	**6** (%)[b]
1	**1j**, m = 1	2	2	61
2	**1j**, m = 1	3	1	73
3	**1k**, m = 2	2	2	56
4	**1k**, m = 2	3	1	50[c]
5	**1l**, m = 0	2	2	42
6	**1l**, m = 0	3	1	42

[a] (a) $Rh(acac)(CO)_2$ (0.5 mol%), BIPHEPHOS (1.0 mol%), pTSA (10 mol%), AcOH, 60 °C. [b] Isolated yield. PMP : 4-paramethoxyphenyl. [c] *E/Z* ratio was determined by ^{1}H-NMR.

Treatment of 3-butenamide **1j** in the cyclized conditions, i.e., $Rh(acac)(CO)_2$ (0.5 mol%), BIPHEPHOS (1 mol%) catalyst in acetic acid at 60 ˚C, successfully afforded the desired single cyclized *E*-enolacetate **6j** in 61% yield (entry 1). Changing the gas ratio of CO and H_2 to 3:1 (4 atm in total) showed slightly increased the yield to 73% (entry 2), accompanied by the **6j'** in 7% yield, which resulted from the formation of a branched aldehyde in hydroformylation. Reaction of 3-butenamide **1k**, bearing a 6-arylhex-5-ynyl group (m = 2), yielded a 2:3 mixture of *E/Z* enolacetate **6k** in 56% (entry 3), [12] while partial pressure slightly decreased to 50% yield (entry 4). Reaction of 3-butenamide **1l**, bearing a 4-arylbut-3-ynyl group (m = 0), afforded only *E* form of indolizidine-typed enolacetate **6l** in 42% yield (entry 5). Changing the partial pressure did not result in a significant yield change (entry 6). The results indicated that the length of the carbon chain in the nucleophile end plays a critical role in the second cyclization. As a result of our investigation, it is concluded that 3-butenamide **1j** is the most suitable for the preparation of the quinolizidine structures.

Basic methanolysis of enolacetate **6j** in the presence of K_2CO_3 afforded *trans*- ketone **7j** in 83% yield, while that of the *E/Z* enolacetate mixture **6k** yielded only single product in 97%, identified as *trans*-ketone **7k**. [14] However, methanolysis of enol-acetate **6l** proceeded very slowly so that an additional amount of base was required (to 50 mol%), and it took 5 days to give *trans*-ketone **7l** in 23% (Scheme 6). The structure of *trans*-ketone **7l** was confirmed by a single crystal X-ray analysis (CCDC no. 987311). Although kinetic controls should not be underestimated because the axial attack of the proton in methanolysis to lead the *trans* ketone, the formation of only *trans* ketone in the basic methanolysis of the three enolacetates **6j~l** suggest thermodynamic control favoring the formation of more stable products.



6j, m = 1.
6k, m = 2; *E/Z*~ 2:3
6l, m = 0.

7j, 83%
7k, 97%
7l, 23%, (CCDC987311)

Scheme 6. Results of basic hydrolysis of enolacetates **6j~l**.

As described above, 3-butenamide, bearing a 5-arylpent-4-ynyl group (m = 1), is the most suitable among the three various substrates in the domino reaction to form quinolizidines with *E*-enolacetate moiety. The method can be also applied to the formation of decahydropyridoazepines (m = 2), but within a pair of *E/Z* diastereomers. It may attribute to that the difference in the

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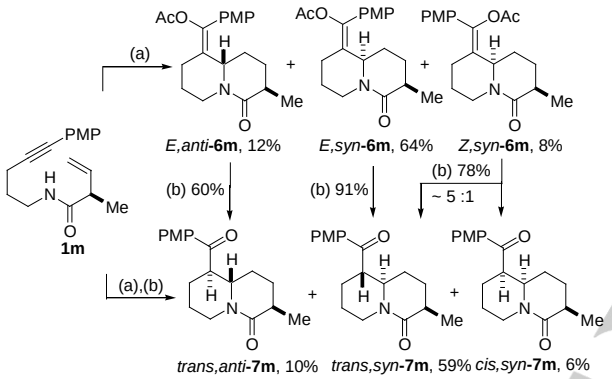
two facial environments in the large ring size is not so obvious that two faces are available for the solvent molecule to produce both possible enolacetates. However, it will not be a critical issue because methanolysis of both *E*- and *Z*-enolacetates will bring the formation of the identical *trans*-ketone products. The results provide a useful guideline that allylamides are better substrates to construct indolizidines while 3-butenamides are suitable to synthesize quinolizidines.

Study on the Diastereoselectivity of 2-Substituted 3-Butenamides: Three different 2-methyl substituted 3-butenamides **1m**~**o** have been synthesized as the substrates to investigate the diastereoselectivity in the reaction. Reaction of **1m** in the cyclization conditions afforded (*E, anti*)-enolacetate **6m** (12%), (*E, syn*)-enolacetate **6m** (64%), and (*Z, syn*)-enolacetate **6m** (8%) (Scheme 7). [15]

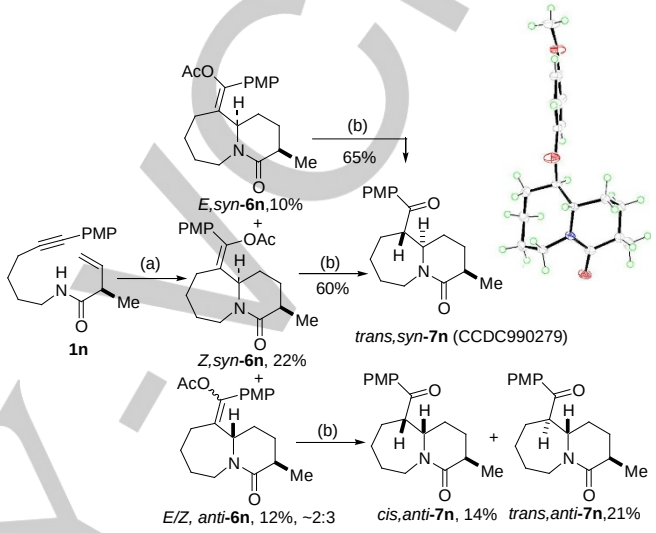


(a) Rh(acac)$(CO)_2$ (0.5 mol%), BIPHEPHOS (1.0 mol%), CO (2 atm), H_2 (2 atm), *p*TSA (10 mol%), AcOH, 60 ^oC (b) K_2CO_3 (10 mol%),MeOH, rt.

Scheme 7. Results of 2-methyl-3-butenamide **1m** in the reactions.

Direct treatment of crude product 6**m** with K_2CO_3 in methanol yielded *trans-anti*-ketone **7m** (10%), *trans-syn*-ketone **7m** (59%) and *cis-syn*-ketone **7m** (6%). Individual methanolysis of (*E, anti*)-enolacetate **6m** led to the formation of *trans-anti*-ketone **7m** as a single product in 60% yield, and reaction of (*E, syn*)-enol-acetate **6m** gave only *trans-syn*-ketone **7m** in 91% yield. However, reactions of (*Z, syn*)-enolacetate **6m** gave a 5:1 mixture of *trans-syn*-ketone **7m** and *cis-syn*-ketone **7m**. It should be noted that the product distribution in the methanolysis of crude enolacetates is consistent with those of individual enolacetates, which suggest the product stability may dominate the distribution in the methanolysis.

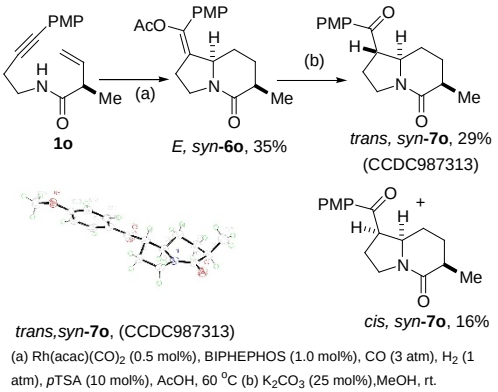
Reaction of 3-butenamide, **1n**, the homolouge of **1m** (m = 2), with one carbon more in the nucleophile side chain afforded all four possible diastereomers, (*E, syn*)-enolacetate **6n** (10%), (*Z, syn*)-enolacetate **6n** (22%) and an inseparable 2:3 mixture of (*E/Z, anti*)-enolacetate **6n** (12%) (Scheme 8). Treatment of (*E, syn*)-enolacetate **6n** with the basic methanol gave a single ketone product in 65%, identified as *trans-syn*-ketone **7n** by single crystal X-ray analysis (CCDC no. 990279). The same ketone was also obtained in 60% yield by treatment of (*Z*, *syn*)-enolacetate **6n** in the basic conditions. Different from single product formation derived from (*E*)- and (*Z*)- *syn*-enolacetates, the methanolysis of (*E/Z, anti*)-enol-acetate mixture **6n** yielded two ketones, identified as the major product *trans-anti*-ketone **7n** in 21% and the minor product *cis-anti*-ketone **7n** in 14%. Treatment of (*E, syn*)-enolacetate **6n** with the basic methanol gave a single ketone product in 65%, identified as *trans-syn*-ketone **7n** by single crystal X-ray analysis (CCDC no. 990279). The same ketone was also obtained in 60% yield by treatment of (*Z*, *syn*)-enolacetate **6n** in the basic conditions.



(a) Rh(acac)$(CO)_2$ (0.5 mol%), BIPHEPHOS (1.0 mol%), CO (2 atm), H_2 (2 atm), *p*TSA (10 mol%), AcOH, 60 ^oC (b) K_2CO_3 (25 mol%),MeOH, rt.

Scheme 8. Results of 2-methyl-3-butenamide **1n** in the reactions.

In the same manner, the reaction of **1o** yielded (*E, syn*)-enol-acetate **6o** as a single product in 35% isolated yield, accompanied by a complex mixture of unidentified side products (Scheme 9).



(a) Rh(acac)$(CO)_2$ (0.5 mol%), BIPHEPHOS (1.0 mol%), CO (3 atm), H_2 (1 atm), *p*TSA (10 mol%), AcOH, 60 ^oC (b) K_2CO_3 (25 mol%),MeOH, rt.

Scheme 9. Results of 2-methyl-3-butenamide **1o** in the reactions.

Treatment of (*E*, *syn*)-enolacetate **6o** within the basic conditions proceeded very slowly as the reaction of **1l** did. It took one week to yielded *cis-syn*-ketone **7o** in 16% yield and *trans-syn*-ketone

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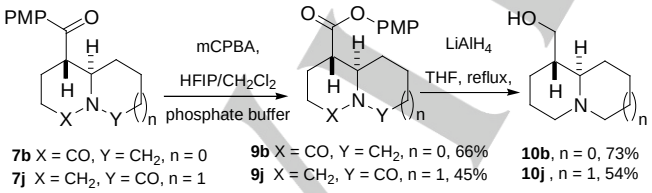
7o in 29% yield, which structure has been confirmed by X-ray crystallography (CCDC no. 987313).

Based on these results, we have reached conclusions that the C-3 position is not a good stereocontrol center in 3-butenamide substrates, the substitution at the C-3 position will result in the formation of several diastereomers. Compared to the reaction results of **1j**, amide **1m** bearing the C-3 methyl group, affords *syn*-enolacetates (i.e., H-3 and the bridged head H-9a) as the major product, and *anti*-enolacetates as the minor product. Individual methanolysis results of quinolizidine enolacetates, (*E, anti*)-**6m**, (*E, syn*)-**6m**, and (*Z, syn*)-**6m**, shows the relative stereochemistry between H-3 and H-9a has been intact during the basic hydrolysis, and the reactions favor the formation of *trans*-ketones (i.e., H-9 and H-9a) as the reaction of **6j** does. The appearance of *cis-syn*-ketone **7m** as the minor product indicates the *syn* configuration between H-3 and H-9a hampers the selectivity for the formation of *trans*-ketone. In the independent methanolysis experiments of enolacetates **6n**, the relative stereochemistry between H-3 and H-10a has been retained in basic hydrolysis as the reaction of enolacetates **6m** did. The presented configuration exerted a significant effect on the subsequent configuration. Here it is worthy to point out that *syn*-enolacetates **6n** is "matched" because of the single *trans*-ketone formation; while *anti*- enolacetates **6n** is "mismatched" because of the formation of both *trans*- and *cis*-ketones.

Applications to tashiroamine and epilupinine: To demonstrate the ability of the methodology, we devised concise syntheses of tashiromine and epilupinine. Tashiromine (**10b**) is a naturally occurring indolizidine which isolated from an Asian deciduous shrub *Maackia tashiroi* (Leguminosae). [16] Thus, ketone **7b** and **7j** underwent the Baeyer-Villiger oxidation using the Uneyamma's protocol, [17] which carried out the reaction in a mixed solvent of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), CH_2Cl_2 and aqueous phosphate buffer solution with mCPBA, affording ester **9b** and **9j** in 66% and 45% yield, respectively. The X-ray crystal structure (CCDC no. 992205) of ester **9j** unequivocally established the *trans* relationship (See supporting information). Simple global reduction of both the ester and the lactam groups with $LiAlH_4$ afforded tashiroamine (**10b**) in 73% yield and epilupinine (**10j**) in 54% yield, whose NMR data were in accordance with literature value[18] (Scheme 10).



Scheme 10. Synthesis of tashiroamine and epilupinine.

Theoretically calculation for the rationale of reactivity difference: Intrigued by the fact that 3-butenamide **1j** could undergo the domino double cyclization but homoallylamide **1i** could not, we carried out DFT calculations on the critical second cyclization of *N*-acyliminium **4**, in which the aryl alkyne moiety react to yield vinyl cation **5**. The results has been modified in the acetic acid conditions. The results provided the corresponding pathway profiles, and located all optimized geometries in the two reactions (Figure 2). The cyclization of **4j** is favored with a relatively lower activation energy barrier of 5.6 Kcal/mol; while the cyclization of **4i** requires a higher activation energy barrier of 7.1 Kcal/mol. An energy difference of 1.8 Kcal/mol between two TSs implied the transition state stability is concerned with the TS geometry. The calculated geometries clearly show both TS geometries possess a boat-like conformation, which results in a remarkable flagpole interaction between H-7axial and H-9a. The distance between H-7axial and H-9a is 2.065 Å in TS_{4i} and 2.333 Å in TS_{4j}, respectively. A closer distance suggests a stronger flagpole conflict, which distorts the HOMO-LUMO intersection angle, and results in the instability of TS_{4i}.

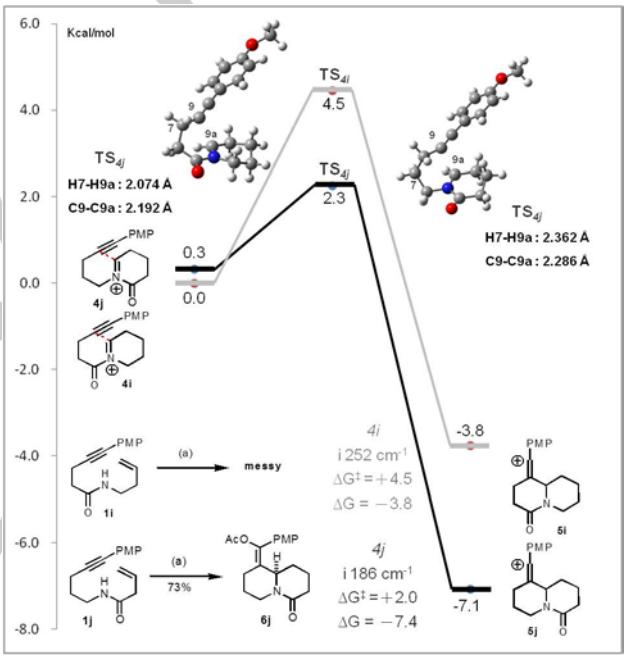


Figure 2. Potential energy diagram of both cyclizations of **4i** and **4j**.

In addition, the intersection angle between the HOMO plane and the LUMO plane is 31.5º for TS_{4i} and 26.7 º for TS_{4j}. [19] A smaller intersection angle guaranteed a better HOMO-LUMO overlapping in TS_{4j} derived from 3-butenamide, supported by relative stability of TS_{4j}. Thus, TS_{4j} derived from 3-butenamides is able to undergo cyclization to yield a quinolizidine but TS_{4i} derived from homoallylamides can not. Thus, acyliminium **4j** which derived from 3-butenamide, is able to undergo the second cyclization to yield the quinolizidine, but **4i** from homoallylamide can not.

Conclusions

We have investigated the alkyne mediated Rh-catalyzed hydroformylation double cyclization reaction of 3-butenamides, which provides cascade syntheses of indolizidines, quinolizidines

and 1-azabicyclo[5.3.0]decanes and 1-azabicyclo[5.4.0] undecanes. The full investigations on the substituted amide substrates revealed the corresponding diastereoselecitivity and the limitation of the double cyclization. It provided useful information for subsequent syntheses. Indolizidine skeleton can be easily achieved by using the reactions of the corresponding allylamides, in which the substitution at both C2 position and C-6 position both provides single product in good yield. Quinolizidine skeleton can be synthesized in good yields from the corresponding 3-butenamide derivatives. The methodology has been successfully applied to 4-step syntheses of tashiromine and epilupinine without protecting groups. In addition, based on the DFT calculation results, the appearance of *trans*-ketone in the methanolysis of enol acetates should attribute to its thermodynamic stability. In addition, the theoretical calculations were also helpful in providing a mechanistic rationale for the successful formation of quinolizidine scaffold from 3-butenamide **1j** due to better HOMO-LUMO overlapping, which changes for the worse in homoallylamide **1i**. Applications of this methodology towards other complex natural products of interest are currently underway.

Experimental Section

General procedure for Domino Hydroformylation/Double Cyclization: $Rh(acac)(CO)_2$ (1.3 mg, 5.0 μmol, 0.5 mol%) and BIPHEPHOS (7.9 mg, 10 μmol, 1.0 mol%) were dissolved in acetic acid (1 mL) under argon. The resulting catalyst solution was degassed by a frozen-thawed procedure at least three times. Amide **1** (257 mg, 1.0 mmol, 1.0 equiv.) and *p*TSA (17 mg, 0.1 mmol, 10 mol%) were placed in a 50 mL flask. The catalyst solution was transferred to the reaction flask containing the substrate by a pipette, and the total volume was adjusted to 20 mL with acetic acid. The reaction flask was placed in a 300 mL stainless steel autoclave and then was pressurized with CO (2 atm) followed by H_2 (2 atm). The reaction mixture was stirred at 60 °C for 16−20 h. Upon completion of the reaction, the gas was carefully released in a good ventilated hood and the reaction mixture was concentrated under reduced pressure to give a crude residue. The residue was partitioned with CH_2Cl_2 (20 mL) and $NaHCO_{3(aq)}$ (saturated, 10 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (15 mL X 5). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to give the crude product. The crude product was purified by flash chromatography on silica gel using MeOH/CH_2Cl_2 or EtOAc/n-Hex as the eluant to give the product.

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Keywords: Domino reaction • Rh-catalyzed Hydroformylation • Indolizidine • Quinolizidine • 1-azabicyclic

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[12] The HSQC experiments show the peaks of δ 4.00 and δ 4.27 are assigned as methines, i.e., H-10a. The nOe irradiation at the peak of δ 4.00 (H-10a) results in an enhancement δ 7.27, while that at the peak of δ 4.27 does not cause any enhancement in the aromatic region. Thus, the peak of δ 4.27 is clearly assigned as *Z*-enolacetate **7c** and that of δ 4.00 as *E*-enolacetate **7c**.

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[14] A large ^1H-^1H coupling constant of 9.6 Hz was observed in both peaks of δ 3.66 (H-10) and δ 4.14 (H-10a), indicating a *trans* arrangement between H-10 and H-10a in ketone **7c**.

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[15] To describe the relative stereochemistry simply, the term of "*trans*/*cis*" was used to describe the configuration of C-9 (or 10 or 8) with C-9 (or 10 or 8)a, i.e., the methine next the ketone, as the 1st notation; and the term of "*anti/syn*" to describe the configuration of C-3 with C-9a, i.e., the bridgehead methine, as the 2nd notation.

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[19] Although it is not easy to read the degree of the HOMO-LUMO overlapping, the orientation of the MO could be expressed as a normal vector of the plane determined by critical nearby atoms. The LUMO orientation could be defined as the normal vector of the plane spanned by iminium nitrogen N-5, proton H-9a and carbon C-1, while the HOMO orientation as the vector of the plane spanned by acetylenic carbon C-9 and the two ortho carbons in the phenyl ring.

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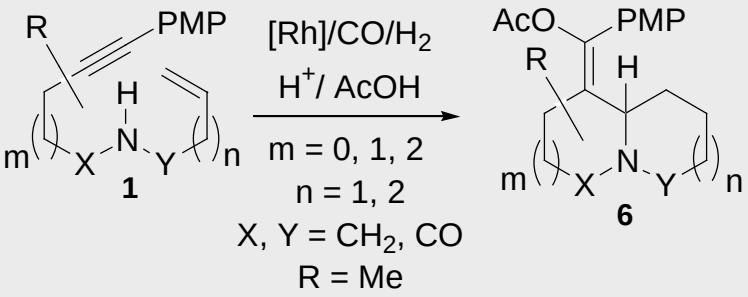

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***Rh-Catalyzed Domino Hydro-formylation Double Cyclizations of* Arylacetylenecarboxamides*: Diastereoselectivity Study and Application for the synthesis of* 1-Azabicyclo[x.y.0]alkanes**