Prolinamide/PPTS-Catalyzed Hajos–Parrish Annulation: Efficient Approach to the Tricyclic Core of Cylindricine-Type Alkaloids

Xiao-Ming Zhang, Min Wang, Yong-Qiang Tu,* Chun-An Fan, Yi-Jun Jiang, Shu-Yu Zhang, Fu-Min Zhang*

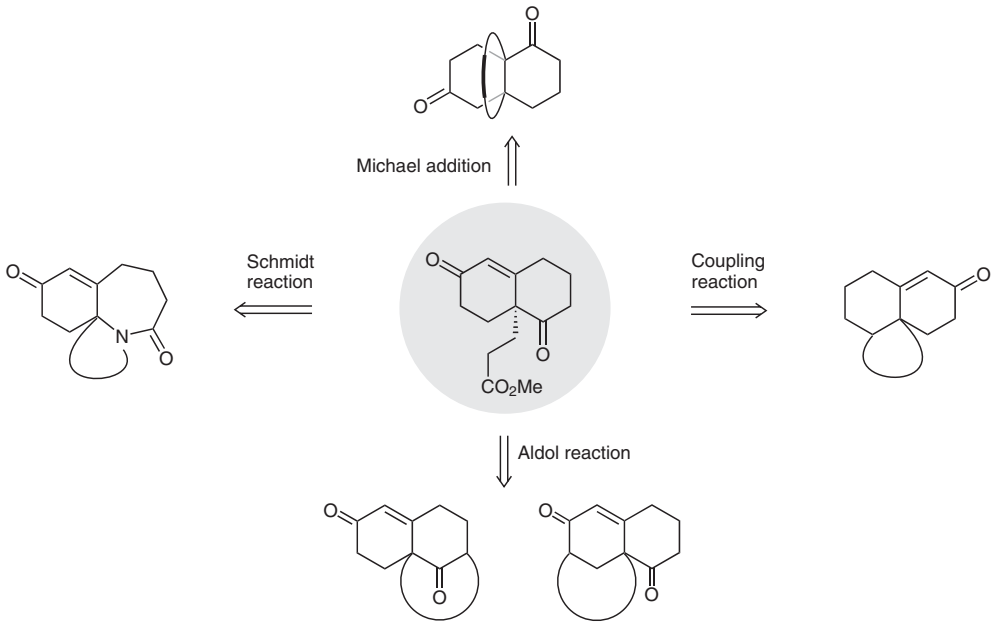
State Key Laboratory of Applied Organic Chemistry & Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. of China
Fax +86(931)8912582; E-mail: tuyq@lzu.edu.cn

Received 20 June 2008

Abstract: A series of Wieland–Miescher ketone analogues bearing highly functionalized substituents are efficiently constructed in high enantioselectivities and good yields using catalytic amounts of prolinamide and PPTS. We have successfully utilized this reaction as a key step to synthesize the tricyclic core of cylindricine type alkaloids.

Key words: prolinamide, Hajos–Parrish annulation, Wieland–Miescher ketone analogues, cylindricine type alkaloids, intramolecular Schmidt reaction

The quaternary 6–6- and 5–6-fused bicyclic systems are core structures incorporated in a variety of biologically significant pharmaceutical molecules and natural products, especially in alkaloids, steroids, and terpenoids, and thus frequently demonstrated as key building blocks in the total synthesis of these interesting molecules.[1] The enantioselective construction of these bicyclic systems has been attracting high attentions since Hajos and Parrish developed L-proline-catalyzed asymmetric Robinson annulation strategy to give access to chiral C8a-methyl 6–6- and 5–6-fused bicyclic species in the early 1970's.[2] From then on, various studies have been performed toward screening the structurally diverse substrates and developing new catalysts to improve the enantioselectivity and reactivity, but most of them only focused on establishing the quaternary fused bicyclic system with simple angular methyl group.[3] In connection with our recent synthetic interests in the polycycle-fused natural products,[4] we realize that the efficient asymmetric construction of the fused bicyclic systems with functionalized chains rather than the simple methyl or ethyl group will give more impact to expeditious synthesis of some natural products with the key tricycle-fused skeletons (Scheme 1),[5] as well as some important pharmaceutical intermedicates.[6] To our knowledge, however, only few examples about the enantioselective access to this kind of synthetic structures were revealed.[7] Recently, our studies on this subject have resulted in more efficient establishment of this kind of fused bicyclic ring system with higher enantioselectivity (up to 88% ee) by using simple and easily available prolinamide and pyridinium *p*-toluenesulfonate (PPTS) as



Scheme 1 Proposed structural diversity of tricyclic systems

SYNLETT 2008, No. 18, pp 2831–2835
Advanced online publication: 15.10.2008
DOI: 10.1055/s-0028-1083542; Art ID: W09908ST

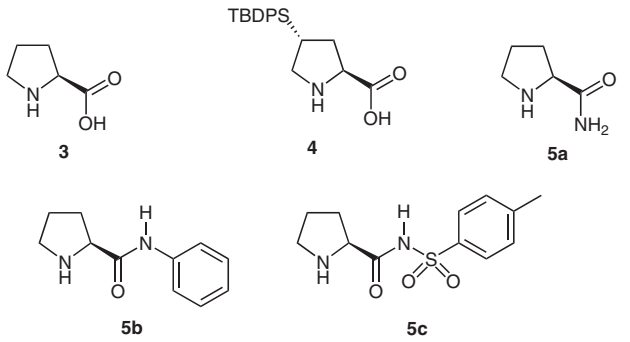
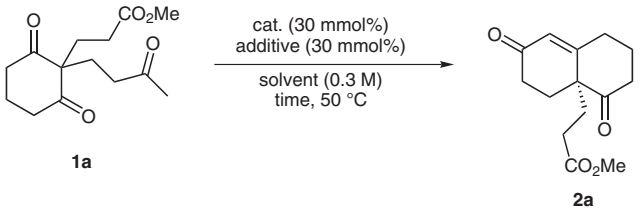


Figure 1 Catalysts screened in asymmetric Hajos–Parrish annulation

combined catalyst, and we have successfully utilized this method to achieve an efficient synthesis of the tricyclic core of cylindricine-type alkaloids. Herein we present our experimental results in detail.

Initially, the substrate **1a** with a C2-propanate ester chain was chosen as a model in the asymmetric annulation to construct the corresponding 6–6-fused bicyclic units by using the easily available catalyst L-proline (**3**, 0.3 equiv, Figure 1) with PPTS (0.3 equiv) in DMF at 50 °C. However, the expected 6–6-fused bicyclic product **2a** was obtained only in 66% ee and 45% yield (Table 1, entry 1).

Table 1 Optimization of Hajos–Parrish Reaction Conditions of **1a**[a]

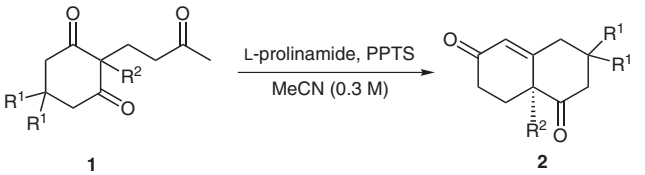


Entry	Catalyst	Solvent	Additive	Time (h)	Yield (%)[b]	ee (%)[c,d]
1	**3**	DMF	PPTS	24	45	66
2	**4**	DMF	PPTS	144	42	61
3	**5a**	DMF	PPTS	144	43	79
4	**5b**	DMF	PPTS	144	32	78
5	**5c**	DMF	PPTS	72	46	76
6	**5a**	DMSO	PPTS	96	50	70
7	**5a**	DCE	PPTS	144	54	81
8	**5a**	MeCN	PPTS	144	65	87
9	**5a**	MeCN	None	144	32	87
10	**5a**	MeCN	PTS	144	42	80
11	**5a**	MeCN	$HClO_4$	144	35	80

[a] Reaction conditions: substrate (0.3 mmol), catalyst (30 mmol%), additive (30 mmol%), solvent (1 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using a Chiralcel OD column.
[d] The absolute configuration was not determined.

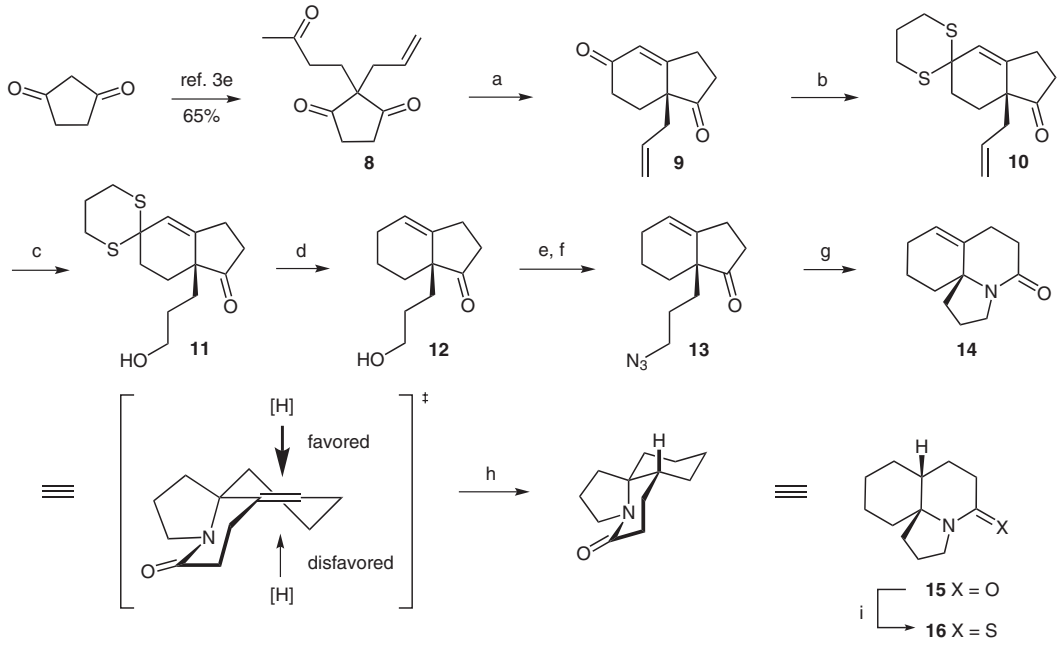
Besides, several L-proline derivatives **4** and **5a–c** were also examined using DMF as the solvent and PPTS as an additive to improve the ee values and the yields of the current reaction. In the review of some literatures on the reactions catalyzed by L-proline and its derivatives, the catalyst **4** has been successfully used in *O*-nitroso-aldol–Michael reaction and Mannich reaction, and **5a–c** have shown high entioselectivity for direct Aldol reactions.[8–10] The further screening results are tabulated in entries 2–11 of Table 1. The employment of **4** only gave the low ee value (61%) and low yield (42%).[9] However, using L-prolinamide (**5a**) or its derivatives **5b** and **5c** (entries 3–5) could dramatically improve the ee values and afford reasonable yields.[10] So L-prolinamide (**5a**) was then subjected to the optimization of reaction media (entries 6–8). From the obtained results, it could be seen that the reaction solvent had an obvious influence on the enantioselectivity and reactivity. For example, using DMSO afforded a higher ee (70%) as well as a better yield (50%), and employing DCE gave much higher ee (81%) in a similar yield (54%). Gratifyingly, while using MeCN as solvent, the best ee (87%) and an improved yield (65%) could be afforded (entry 8). Finally, the effect of the additive was also examined. The parallel reaction without any additive only gave the desired product in low yield (32%), but could maintain the enantioselectivity (80% ee, entry 9). While using other additive such as PTS and $HClO_4$, there was no improvement for the ee and the yield (entries 10 and 11).

Table 2 L-Prolinamide-Catalyzed Hajos–Parrish Reaction of Various 1,3-Diones[a]



Entry	Substrate	Product	Yield (%)[b,e]	ee (%)[c–e]
1	**1a**, R^1 = H, R^2 = $CH_2CH_2CO_2Me$	**2a**	65	87
2	**1b**, R^1 = H, R^2 = $CH_2CH_2CO_2Et$	**2b**	51	82
3	**1c**, R^1 = H, R^2 = $CH_2CH_2CO_2n$-Bu	**2c**	57	82
4	**1d**, R^1 = Me, R^2 = $CH_2CH_2CO_2Me$	**2d**	41	70
5	**1e**, R^1 = H, R^2 = allyl	**2e**	56	85[f]
6	**1f**, R^1 = H, R^2 = $CH_2CBr{=}CH_2$	**2f**	46	83
7	**1g**, R^1 = H, R^2 = CH_2CH_2CN	**2g**	59	88
8	**1h**, R^1 = H, R^2 = Me	**2h**	68	87
9	**1i**, R^1 = H, R^2 = Et	**2i**	70	86
10	**1j**, R^1 = H, R^2 = Bn	**2j**	56	86

[a] See Experimental Section.
[b] Isolated yield.
[c] Determined by chiral HPLC (see the Supporting Information for detail).
[d] The absolute configuration was not determined.
[e] Reaction conditions: L-prolinamide (30 mmol%), PPTS (30 mmol%), MeCN (0.3 M), 50 °C.
[f] The absolute configuration *R* was assigned by the comparison of the known optical rotation value.



Scheme 2 *Reagents and conditions*: (a) D-prolinamide (0.3 equiv), PPTS (0.3 equiv), MeCN, 50 °C, 60%, 83% ee; (b) $HS(CH_2)_3SH$ (1.1 equiv), TMSCl (0.3 equiv), $CHCl_3$, r.t., 75%; (c) $BH_3{\cdot}SMe_2$ (1 equiv), cyclohexene (2 equiv), THF, 0 °C, then $NaBO_3{\cdot}4H_2O$, H_2O, r.t., 95%; (d) W-2 Raney Ni, EtOH, r.t., 82%; (e) MsCl (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, r.t.; (f) NaN_3 (5 equiv), DMF, r.t., 87% over 2 steps; (g) $BF_3{\cdot}OEt_2$, r.t., 70%; (h) H_2, Pd/C, EtOAc, r.t., 83%; (i) Lawesson's reagent (0.75 equiv), toluene, reflux, 96%.

Under the optimized conditions, a variety of 1,3-cyclohexanedione substrates were examined. As shown in Table 2, the substrates bearing various of propanate esters **1b–c** (entries 1–3) gave the expected Wieland–Miescher ketone analogues **2b–c** in high enantioselectivities and good yields, while **1d** bearing two methyl groups at the six-membered ring gave a lower ee of 70% and a yield of 40% (entry 4). Similar results were also obtained in the cases of dione substrates **1e** and **1f** with allyl or 2-bromoallyl group, respectively (entries 5 and 6).[11] In addition, the cyano dione **1g** also proved to be well effective in this reaction, and gave the highest ee value (88%, entry 7). Furthermore, the well-known substrate, 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**1h**), was examined (entry 8), and it proceeded smoothly to afford the expected product **2h** in 87% ee in 68% yield, being better than the very recent literature report (78% ee, 57% yield).[3b] Finally, when ethyl- or benzyl-substituted substrates **1i** and **1j** were subjected to this annulation, similar ee values could also be obtained (entries 9 and 10). These results indicated that the substitution at the six-membered ring of the 1,3-dione substrate has some influence on the enantioselectivitiy and the yield of this reaction, but the property of functionalized carbon chain at C-2 position has no significant influence.

After we had established this kind of fused bicyclic ring system with higher enantioselectivity, we tried to utilize this method to construct the core tricyclic structure of cylindricine-type alkaloids. The cylindricines were isolated by Blackman from the Tasmanian ascidian *Clavelina cylindrica* in 1993.[12] Further investigations showed their toxicity in a brine shrimp assay.[12] Part of these alkaloids

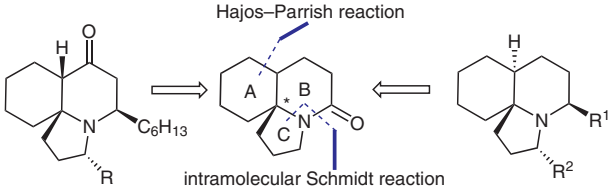


Figure 2 Some cylindricines and lepadiformines

6a–e, along with the lepadiformines **7a–c** isolated by Biard's group in 1994,[13] possess a novel tricyclic core and some other important biological activities.[13] Due to their unique structures, lots of synthetic efforts appeared after their isolation and most of them focused on strategies to form the key tricyclic ring system.[14]

As shown in Figure 2, our strategy was featured by the current prolinamide/PPTS-catalyzed Hajos–Parrish annulation and an intramolecular Schmidt reaction,[15] establishing the fused A,B,C-ring system.

Our synthesis commenced with substrate **8** (Scheme 2), which could be easily accessed from 1,3-cyclopentadione in a higher yield than Landais and Vincent's conditions (up to 65% over two steps).[16]

When we treated **8** with a catalytic amount of D-prolinamide under the optimized conditions, the desired intermediate **9** could be obtained with 83% ee in 60% yield. Direct Brown hydroboration of **9** gave a sluggish reaction

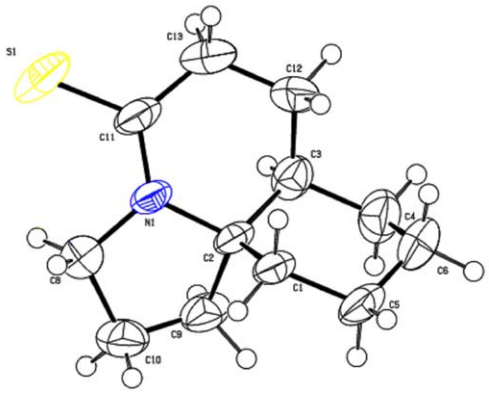


Figure 3 X-ray crystal structure of **16**

mixture.[17] Therefore we first protected the carbonyl group of α,β-unsaturated enone of **9** to afford **10**,[18] then under Kabalka's conditions,[17] the Brown hydroboration elaborated **11** in good chemo- and regioselectivity as well as high yield (up to 95%). Reduction of the thioether **11** with W-2 Raney Ni in EtOH delivered **12**. Conversion of the hydroxyl group of **12** to its methylsulfonate ester, followed by the substitution of azide provided **13** in 87% yield over two steps. At this stage, we attempted the crucial intramolecular Schmidt reaction to construct the third ring.[15] A variety of experiments were conducted, with a particular emphasis on the Lewis acid and the solvent. Both $TiCl_4$ in CH_2Cl_2 and $BF_3{\cdot}OEt_2$ in Et_2O or CH_2Cl_2 could promote the reaction, but the yield was low (around 40–50%). Finally, we found that when the reaction was carried out with $BF_3{\cdot}OEt_2$ without any solvent, the lactam product **14** could be obtained in up to 70% yield. Catalytic hydrogenation of the C–C double bond of **14** afforded the tricyclic core **15**.

As we expected, the catalytic hydrogenation proceeded from a less hindered side of the double bond. The relative configuration between A and B rings in **15** was determined to be same as the natural occurring cylindricine-type alkaloids, and it was further confirmed by X-ray analysis of **16** (Figure 3) which was derived from **15** under Lawesson's conditions.[19,20]

In summary, we have demonstrated that prolinamide/PPTS is an effective catalyst for the Hajos–Parrish reaction. This desymmetric annulation can be applied to the efficient and enantioselective synthesis of 6–6- or 5–6-fused Wieland–Miescher ketone analogues, especially bearing the functionalized quaternary angular chain. Finally, we have successfully applied this method to an expeditious asymmetric construction of the tricyclic core of cylindricines.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We are grateful for the financial support of the NSFC (Nos. 20672048, 20621091 and 20732002) and the Chang Jiang Scholars Program. We thank Mr. Yongliang Shao for X-ray analysis of compound **16**.

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