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Intramolecular Pauson–Khand reaction of optically active aza-Baylis–Hillman adducts

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ABSTRACT

The intramolecular Pauson–Khand reaction of aza-Baylis–Hillman adducts, which were prepared through the thio-Michael/imino-aldol domino reaction of optically active sulfinimines, was examined and gave optically active *cis*- and *trans*-pyrrolidine-fused cyclopentenones in a stereoselective manner.

The aza-Baylis–Hillman reaction is one of the most potentially useful synthetic methods because it provides β-amino-α-methylene esters, which are regarded as useful synthetic building blocks, in one step from α,β-unsaturated carbonyl compounds and imines.[1] Although a number of reports have been published for the catalytic asymmetric modification of aza-Baylis–Hillman reaction, so far most examples are limited to the use of aromatic imines and only a few examples are successfully applicable to aliphatic imines.[2] To overcome this drawback, we have recently developed a useful preparation of optically active aza-Baylis–Hillman adducts via the thio-Michael/imino-aldol domino reaction of chiral sulfinimines, which gives aza-Baylis–Hillman adducts derived from aliphatic imines in a highly enantioselective manner.[3a] This is a promising methodology because of its usefulness in the conversion of a wide range of aliphatic imines to chiral aza-Baylis–Hillman adducts. We have already applied the transformation to the synthesis of heterocyclic compounds, and successfully achieved the formal synthesis of (−)-trachelanthamidine.[3b] The formed chiral β-amino esters would also be useful for the preparation of pyrrolidine ring-fused cyclopentenones through the intramolecular Pauson–Khand reaction, which is recognized as a powerful tool for the construction of cyclopentenone frameworks through [2+2+1] cyclizations.[4] The reaction has received much attention due to its potential applicability in the synthesis of complex molecules.[5] Although the original cobalt complex-catalyzed Pauson–Khand reaction requires an excess of $Co_2(CO)_8$ to proceed to completion,[4] various catalytic Pauson–Khand reactions with using other transition metals have been reported in the past decade. We thought that the optically active aza-Baylis–Hillman adducts prepared using our methodology would provide good precursors for the intramolecular Pauson–Khand reaction after facile N-propargylation. To our knowledge there are few such examples of the Pauson–Khand reaction starting from chiral aza-Baylis–Hillman adducts. In this Letter, we describe a new process to carry out intramolecular Pauson–Khand methodology through optically active aza-Baylis–Hillman adducts derived from aliphatic imines. The method will provide a potentially useful synthesis of aza-heterocyclic compounds. It is remarkable that an alkyl substituent at the C3 position induced cis-selectivity in the Pauson–Khand reaction products preferentially; the selectivity is opposite to similar Pauson–Khand reactions starting from other electron-deficient alkenes.[6,5c]

The optically active aza-Baylis–Hillman adducts **1** were prepared from chiral sulfinimines and *tert*-butyl acrylate by the procedure previously reported.[3a] The conversion to intramolecular Pauson–Khand precursors **3** was achieved through S-oxidation to sulfonamines **2** followed by propargylation under basic conditions (Scheme 1).[3b] For example, the adduct **1a**, obtained in 57% yield (94% de) through the domino reaction, was oxidized by treatment with *m*-CPBA at room temperature to give sulfonamine **2a** in 97% yield. The N-propargylation of **2a** gave the Pauson–Khand precursor **3a** in 84% yield. The enantiomeric excess of **2a** was estimated to be 92%, which was determined by HPLC analysis with ChiralPak IC (entry 1). The optical purity of these compounds was almost the same and no significant epimerization occurred during the transformation. The results are summarized in Table 1.

With desired precursors **3** in-hand, we examined the Pauson–Khand reaction of **3a** under various conditions. Commercially available $Co_2(CO)_8$ was used as a catalyst (Scheme 2). The results are summarized in Table 2. The use of 100 mol % of $Co_2(CO)_8$ provided the desired adduct **4a** in 77% yield, while the reduction of catalyst amounts to 60 mol % decreased the yield **4a** to 19% (entries 1 and 2). To improve the yield of **4a**, we applied Yang's reaction conditions[7] and employed 60 mol % of (*N*,*N*,*N*,*N*)-tetramethylthiourea (TMTU); adduct **4a** was isolated in 85% yield (entry 4). Thus, a reduction of the amount of $Co_2(CO)_8$ was successfully achieved when a sufficient amount of TMTU coexisted in the reaction mixture. For example, when the amount of $Co_2(CO)_8$ was reduced to 10 mol % compound **4a** was obtained in 84% yield provided that 60 mol % of TMTU was present in the reaction mixture (entry 5).

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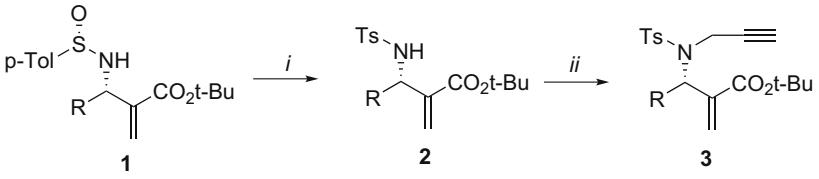


Scheme 1. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, rt; (ii) propargyl bromide, K_2O_3, DMF.

Table 1
Preparation of intramolecular Pauson–Khand precursors **3**

Entry	R	**2**; Yield[a] (%)	**3**; Yield[a] (%)
1	Pr	**2a**; 97 (92)	**3a**; 84 (92)
2	Bu	**2b**; 82 (92)	**3b**; 86 (92)
3	*i*-Bu	**2c**; 97 (99)	**3c**; 82 (99)
4	*i*-Pr	**2d**; 100 (96)	**3d**; 86 (94)
5	*c*-C_6H_{11}	**2e**; 90 (94)	**3e**; 90 (94)
6	*p*-Tol	**2f**; 92 (99)	**3f**; 84 (92)
7	*p*-ClC_6H_4	**2g**; 98 (99)	**3g**; 94 (92)

[a] Isolated yield. Enantiomeric excesses are in parentheses. Ee values were determined by HPLC analyses (ChiralPak-IC, hexane/2-propanol 80:20).

Table 2
The Pauson–Khand reaction of **3a**

Entry	$Co_2(CO)_8$ (mol %)	TMTU (mol %)	**4a**; Yield (%)[a]
1	100	0	77
2	60	0	19
3	60	10	59
4	60	60	85
5	10	60	84

[a] Isolated yield.

Table 3
The Pauson–Khand reaction of **3**

Entry	R	**4**	Yield[a] (%)	cis/trans[b]
1	Pr	**4a**	85 (86)	75/25
2	Bu	**4b**	62 (90)	77/23
3	*i*-Bu	**4c**	66 (96)	74/26
4	*i*-Pr	**4d**	45 (96)	86/14
5	*c*-C_6H_{11}	**4e**	59 (90)	80/20
6	*p*-Tol	**4f**	83 (94)	37/63
7	*p*-ClC_6H_4	**4g**	82 (90)	29/71

[a] Isolated yield. Enantiomeric excesses for major isomer are in parentheses. Ee values were determined by HPLC analyses (ChiralPak-IC, hexane/2-propanol 80:20).
[b] Determined by ^1H NMR.

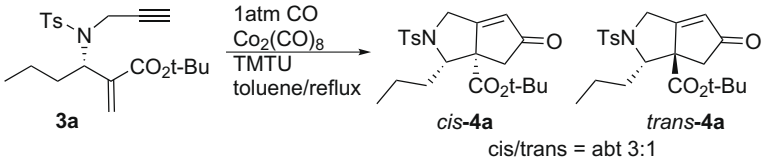
However, the reaction under these conditions was unreproducible unless freshly opened dicobalt complex was used. This is probably due to the slow decomposition of $Co_2(CO)_8$. Therefore, we used 60 mol % of $Co_2(CO)_8$ in order to examine the generality of the reaction.

The cyclization of other precursors also took place smoothly (Scheme 3). The results are summarized in Table 3.[8] For example, the Pauson–Khand product **4b** was obtained in 62% yield (entry 2). Compound **4b** was obtained as a mixture of two stereoisomers, whose ratio was estimated to be 77/23 by ^1H NMR analysis. Chiral HPLC analysis revealed that the optical purity of the major isomer of **4b** was estimated to be 90% ee. This value was slightly lower than the ee value of the starting material **3b** (92% ee). Thus, the discussed procedure provided optically active bicyclic compounds from asymmetric aza-Baylis–Hillman adducts. The diastereoselectivity of the reactions was about 3:1 for compounds that had primary alkyl groups at the R position (entry 1–3), and 4:1 or 7:1 for the compounds that had secondary alkyl groups at the R position (entry 4 and 5). It is remarkable that cis-selectivity was observed in the intramolecular Pauson–Khand reaction. This selectivity was opposite to that reported by Ichikawa and co-workers, who showed that the reaction progressed dominantly in a C3–C3a trans-selective manner.[5c] On the other hand, when an aromatic group occupied the R position, trans-selectivity was observed (entries 6 and 7). For example, the Pauson–Khand adduct **4f** was obtained in 83% yield as a mixture of cis/trans isomers in a ratio of 37:63. Thus, the stereoselectivity of the intramolecular Pauson–Khand reaction depended on the R substituent, and the selectivity was switched from cis to trans as the substituent at the R position changed from aliphatic to aromatic.

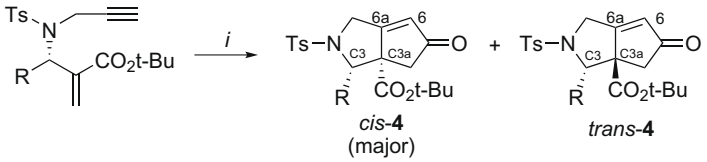
The stereochemistry of the adduct **4** was determined by X-ray crystallographic analyses. For example, compound **4e** contained two diastereomers, which were separated by careful flash column chromatography. The major isomer of **4e** gave good crystals for X-ray analysis, which indicated a *cis* configuration between C3 and C3a unambiguously.[9] The major isomer of **4g** was also isolated and X-ray analysis clearly showed a trans configuration between C3 and C3a positions.[10]

It should be mentioned that the ^1H NMR signal at the C6 position (the vinylic proton in α,β-unsaturated alkene unit) in the cis-isomers showed a remarkable upfield shift. For example, these signals appeared at 5.25 ppm for *cis*-**4e** and 4.5 ppm for *cis*-**4f**, while they appeared around 6.1 ppm for the corresponding trans isomers. X-ray crystallographic analysis for *cis*-**4e** and *trans*-**4g** clearly showed that the protons in the *cis*-isomer are located above the plane of the phenyl ring of the *N*-tosyl group and the strongly affected by the ring current of the aromatic ring. Thus, it is expected that the preferred conformation of the cis-isomer will offer a very good bias for controlling a nucleophilic attack at the C6a carbon. An investigation of this is underway.

In conclusion, we have succeeded in forming pyrrolidine ring-fused cyclopentenones by means of an intramolecular



Scheme 2.



Scheme 3. Reagents and conditions: (i) 60 mol % $CO_2(CO)_8$, 60 mol % TMTU, 1 atm CO, toluene, reflux, 16 h.

Pauson–Khand reaction starting from readily available optically active aza-Baylis–Hillman adducts. The stereoselectivity of the reaction depended on the R substituent; a moderate to high cis-selectivity is obtained when an alkyl group is placed at the R position, while an approximate ratio of 1:2 is obtained for the trans-isomer when an aromatic group occupies the R position. Further investigations to elaborate the scope and extend the applications of this methodology are in progress in our laboratory.

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8. *The Pauson–Khand reaction of* **3e***: typical procedure.* Under CO atmosphere, a mixture of **3e** (155.8 mg, 0.36 mmol), TMTU (28.7 mg, 0.22 mmol), and $Co_2(CO)_8$ (75.6 mg, 0.22 mmol) in degassed toluene (10 mL) was heated at refluxing temperature for 16 h. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (silica gel/hexane–EtOAc 10:1 then 5:1) to give **4e** in 59% yield (97.1 mg). *trans*-**4e** and *cis*-**4e** were separated by further careful chromatography. *trans*-**4e**: oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.10 (s, 1H), 4.64 (d, J = 4.3 Hz, 1H), 4.22 (d, J = 16.4 Hz, 1H), 4.09 (d, J = 16.4 Hz, 1H), 3.08 (s, 1H), 2.57 (d, J = 17.8 Hz, 1H), 2.52 (d, J = 17.8 Hz, 1H), 2.40 (s, 3H), 1.76–1.56 (m, 4H), 1.50–1.04 (m, 7H), 1.23 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.4, 177.6, 169.4, 143.5, 136.1, 129.4, 127.9, 126.5, 83.1, 66.7, 63.8, 46.9, 44.3, 43.1, 40.6, 31.9, 28.6, 27.4, 26.2, 26.0, 21.4. *cis*-**4e**: white solid; mp 127.8–128.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 5.25 (s, 1H), 4.53 (d, J = 15.4 Hz, 1H), 4.32 (d, J = 15.4 Hz, 1H), 3.36 (d, J = 8.6 Hz, 1H), 3.22 (d, J = 17.2 Hz, 1H), 2.40 (s, 3H), 2.05–1.62 (m, 8H), 1.43 (s, 9H), 1.27–1.05 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3, 174.5, 168.5, 144.6, 134.0, 129.7, 127.8, 124.1, 83.6, 74.2, 62.8, 50.4, 48.2, 40.5, 30.9, 29.9, 27.7, 26.5, 26.2, 26.1, 21.4; Anal. Calcd for $C_{25}H_{33}NO_5S$: C, 65.33; H, 7.24; N, 3.05. Found: C, 65.03; H, 7.20; N, 3.02.
9. Crystallographic data (excluding structure factors) for the structures *cis*-**4e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC759538. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Crystallographic data (excluding structure factors) for the structures *trans*-**4g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC759539. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].