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Organocatalytic Enantioselective Michael–Michael–Henry Reaction Cascade. An Entry to Highly Functionalized Hajos–Parrish-Type Ketones with Five to Six Contiguous Stereogenic Centers and Two Quaternary Carbons

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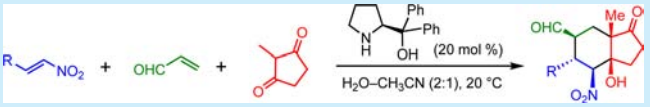
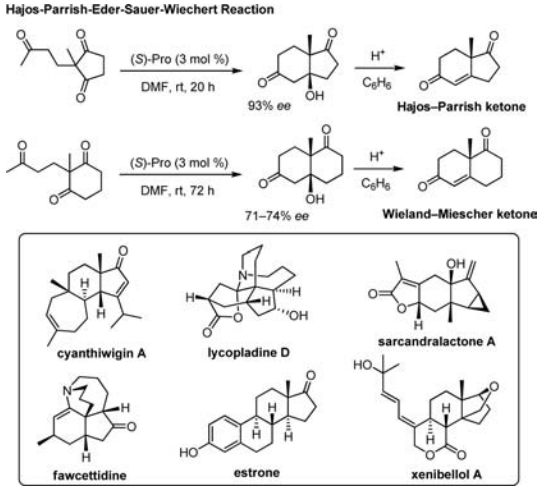
Supporting Information

ABSTRACT: An organocatalytic enantioselective reaction of 2-methylcyclopentane-1,3-dione, nitroalkene, and α,β-unsaturated aldehyde with the diphenylprolinol catalyst was developed to give the highly functionalized Hajos–Parrish-type ketones with five to six contiguous stereocenters and two quaternary carbon stereogenic centers with high diastereoselectivity and enantioselectivity. The structures of the adducts were unambiguously confirmed by single-crystal X-ray crystallographic analyses of the appropriate products.

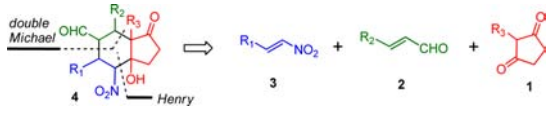


Contemporary synthetic chemistry has enjoyed great accomplishments in the development of asymmetric organocatalysis. Among these synthetic methods, the organocatalytic C–C bond-forming reaction in cascade reactions[1] or one-pot operations has effectively advanced molecular complexity. The Hajos–Parrish–Eder–Sauer–Wiechert reaction (HPESW reaction),[2] known as a milestone of asymmetric catalysis and one of the historical origins of organocatalysis, has provided the enantiomerically enriched Wieland–Miescher ketone (WMK)[3] and Hajos–Parrish ketone (HPK)[4] as adaptable building blocks for organic synthesis (Scheme 1). Since its discovery 40 years ago, the HPESW reaction has been particularly important. Not only has this reaction been employed in numerous syntheses of complex terpene natural products, steroids, and medicinal drugs, but it also has led to the development of organocatalysis and has contributed to the robust research of modern asymmetric synthesis in the present century. Despite these advances, a multicomponent[5] enantioselective one-pot cascade reaction employing 2-methylcyclopentane-1,3-dione in the synthesis of highly functionalized HPK analogues, especially those with nitro substitutents, has not yet been achieved.[6] To the best of our knowledge, the organocatalytic reaction of 2-alkylcyclopentane-1,3-dione with nitroalkene[7] has not been reported.[8] Consequently, such an asymmetric catalytic cascade reaction for the synthesis of highly functionalized HPK analogues is unprecedented and is a compelling subject of investigation. In the context of this background and in an effort to extend our interest[9] in multicomponent organocatalytic asymmetric annulations[10] with cascade reactions[11] or one-pot operations,[12] we envisaged that a double Michael–Henry cascade of organocatalytic reactions of 2-alkylcyclopentane-1,3-dione (**1**), α,β-unsaturated aldehyde (**2**), and nitroalkene (**3**) might provide an appropriate protocol for the construction of highly functionalized HPK (**4**) containing six contiguous stereogenic centers (Scheme 2).[13] While the idea is straightforward and the preceding intra-

Scheme 1. HPESWR Reactions and Selected Examples of the Synthesis of Natural Products Employing the Hajos–Parrish Ketone and Its Analogues



Scheme 2. Retrosynthetic Analysis



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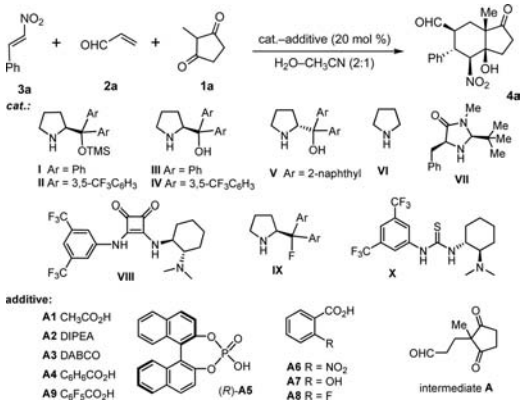
molecular HPESW reaction has been demonstrated in many variants, and even though the cascade intermolecular reaction with cyclopentane-1,3-dione remains elusive, other factors may impede the development of such a reaction sequence. New and specific methodology may be required for the efficient assembly of the requisite cyclopentane-1,3-dione. Herein, we report a solution to overcome the obstacle of preparing this compound with a multicomponent and cascade operation.

Some crucial factors affecting the feasibility of the reaction include: (1) the extremely low solubility of 2-methylcyclopentane-1,3-dione (**1a**) in most organic solvents; (2) the nature of **1a** to act as a leaving group, causing the reverse reaction of the Michael adduct;[14] and (3) the requirement for a sufficient catalyst for proper conversion and stereoselectivity. Since **1a** dissolved well in water, a cosolvent system of water and organic solvent was selected as the reaction media for the investigation.[15] Initially, the reaction of **1a**, acrolein (**2a**), and nitrostyrene (**3a**) with 20 mol % of Jørgensen–Hayashi catalyst (**I**)[16] and acetic acid in H_2O–CH_3CN (2:1) at ambient temperature for 3 days gave 51% yield of adduct **4a** with a moderate ee of 66% (Table 1, entry 1). The same reaction conditions with catalyst **II** and acetic acid gave only the Michael intermediate **A** and recovery of **3a** after one-week of reaction (Table 1, entry 2). Encouragingly, the reaction with **III**–HOAc for 84 h afforded 73% yield of **4a**, with 85% ee (Table 1, entry 3). Alternatively, the reaction with **IV**–HOAc gave moderate yields and ee, and the reaction with (*R*)-di-2-naphthylprolinol (**V**)–HOAc did not improve the ee but gave lower yields (Table 1, entries 4 and 5). On the other hand, the reaction with pyrrolidine (**VI**)–HOAc provided only 27% yield (Table 1, entry 6), and the reaction with MacMillan catalyst (**VII**)–HOAc or squaramide **VIII** gave only the Michael intermediate **A** and recovered **3a** after many days of reaction (Table 1, entries 7 and 8). Additionally, the reaction catalyzed by fluorocatalyst **IX** (20 mol %) gave moderate ee (Table 1, entry 9). Screening of the catalyst **I** or **III** with a variety of additives did not afford better yields or ee (Table 1, entries 11–18). Notably, addition of base, e.g., DIPEA or DABCO, facilitated the reaction but gave lower yields and enantioselectivities (Table 1, entries 11 and 12). The reactions catalyzed by **III**–HOAc in the cosolvent system of water[17] and various solvents, e.g., toluene, CH_2Cl_2, THF, MeOH, in different ratios, were scrutinized, and the H_2O–CH_3CN (2:1) system was the best choice. When the reaction temperature was decreased to 20 °C from ambient temperature, the enantioselectivity of **4a** was slightly increased from 85% to 88%, but it required longer time (8.5 days vs 3.5 days)[18] for the completion of the reaction (Table 1, entries 19 and 3, respectively). Interestingly, in the presence of catalyst **III** alone and without any additive, the reaction rate was somewhat facilitated with slightly better yield and ee (Table 1, entry 20). Conducting the reaction under less concentrated conditions (0.1 M) required a much longer time for the reaction and afforded lower yield (Table 1, entry 21). Therefore, the reaction with 20 mol % of diphenylprolinol (**III**) at 20 °C stood out as the best reaction conditions (Table 1, entry 20). The structure of **4a** was determined by X-ray crystallographic analysis (Figure 1).

With the optimized reaction conditions in hand, the reaction was screened with a series of nitrostyrenes **3**. The reaction was quite general with respect to the various nitrostyrenes and gave good yields with high enantioselectivities, 90–94% ee (Table 2). Most reactions were completed within 2–3 days and took several additional days for the complete isomerization of the diastereoisomer (vide infra) to afford adduct **4** as the only isolable stereoisomer and the only distinguishable isomer in the crude ^{1}H NMR spectrum (dr >20:1). Incidentally, the reaction with the 4-chloro- and 4-bromo-substituted nitrostyrenes (**3d**

Table 1. Screening of the Catalysts, Additives, Solvents, and Reaction Conditions for the Cascade Reactions[a]



entry	cat.	additive	time (d)	yield[b] (%)	ee[c] (%)
1	**I**	**A1**	3	51	66
2	**II**	**A1**	7	~0[d]	na
3	**III**	**A1**	3.5	73	85
4	**IV**	**A1**	10	30	35
5	**V**	**A1**	4	39	−85
6	**VI**	**A1**	5	27	0
7	**VII**	**A1**	7	~0[d]	na
8	**VIII**		5	~0[d]	na
9	**IX**		4	70	61
10	**I**–**X**	**A1**	2.5	50	83
11	**I**	**A2**	2.5	39	38
12	**I**	**A3**	2	35	46
13	**III**	**A5**	7	~0[d]	na
14	**III**	**A4**	3	72	83
15	**III**	**A6**	3.5	69	85
16	**III**	**A7**	3	70	84
17	**III**	**A8**	3	69	86
18	**III**	**A9**	7	<5	nd
19[e,f]	**III**	**A1**	8.5	71	88
20[e,f]	**III**		7.5	75	91
21[f,g]	**III**		16	66	90

[a]Unless otherwise noted, the reactions were performed on a 0.3 M scale of **1a** (1.0 equiv), **2a** (1.5 equiv), and **3a** (1.2 equiv) with 20 mol % of catalyst in H_2O–CH_3CN (2:1) at ambient temperature (~25–30 °C). [b]Yields of **4a** isolated. [c]Determined by HPLC with a chiral column (Chiralpak IC). [d]No product **4a** was observed; only intermediate **A** and the recovery of nitrostyrene **3a** were observed. [e]20 °C. [f]**1a** (2.5 equiv), **2a** (2.5 equiv), and **3a** (1.0 equiv). [g]The reaction was performed on a 0.1 M scale of **1a**. na = not available. nd = not determined.

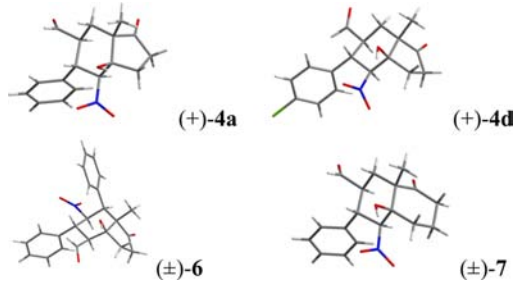


Figure 1. Stereoplots of the X-ray crystal structures of (+)-**4a**, (+)-**4d**, (±)-**6**, and (±)-7. Key: : C, gray; O, red; N, blue; Cl, green.

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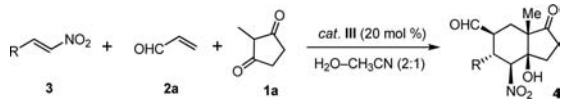
Table 2. Example of Cascade Michael–Michael–Henry Reaction[a]



3 2a 1a 4

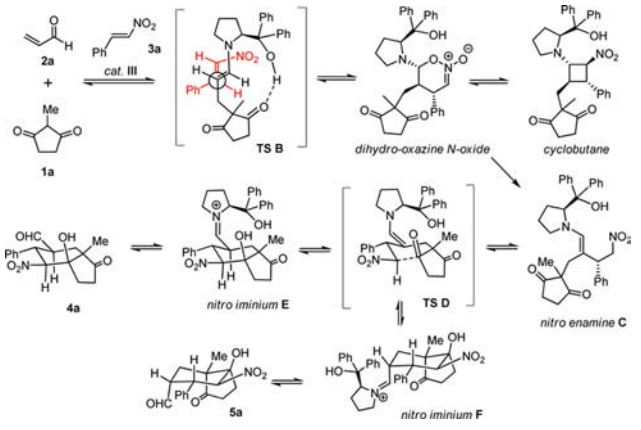
entry	4	R	time[b] (d)	yield[c] (%)	ee[d] (%)
1	**4a**	Ph	7.5	75	91
2	**4b**	4-F-Ph	8	74	94
3	**4c**	4-Me-Ph	10	72	94
4	**4d**	4-Cl-Ph	12[e]	58	93
5	**4e**	4-Br-Ph	14[e]	59	91
6	**4f**	4-OMe-Ph	9	66	91
7	**4g**	4-Et-Ph	9	69	90
8	**4h**	3-F-Ph	7	70	93
9	**4i**	2-furyl	7	71	91
10	**4j**	2-F-Ph	7.5	65	93

[a]Unless otherwise noted, the reactions were performed on a 0.3 M scale of **1a** (2.5 equiv), **2a** (2.5 equiv), and **3** (1.0 equiv) in H_2O–CH_3CN (2:1) at 20 °C and time. [b]Unless otherwise noted, the reaction was completed in ca. 48 h to give **4** and its isomer **5**, and the rest of the time was required for the complete isomerization of diastereomer (e.g., **5a**) to give **4**, vide infra. [c]Yields of **4** isolated. [d]Determined by HPLC with a chiral column (Chiralpak IC). [e]Reaction was completed in 6 days, and the rest of the time was required for the complete isomerization.

and **3e**) required longer reaction time to complete the reaction (probably due to the low solubility of **3d** and **3e** in the reaction media) and afforded lower yields (Table 2, entries 4 and 5). The structure and the absolute configuration of (+)-**4d** was unambiguously assigned by X-ray analysis of its single crystal (Figure 1).

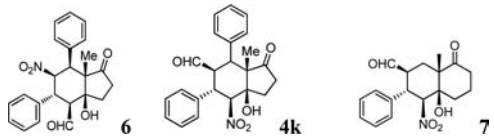
To account for the chemoselectivity and stereoselectivity of the reactions, we proposed a plausible mechanism as depicted in Scheme 3. Initial Michael addition of **1a** to acrolein generated

Scheme 3. Plausible Reaction Mechanism



intermediate **A**, followed by conjugate addition of enamine-activated aldehyde **A** under the control of the diphenylprolinol catalyst (**TS B**)[19] to give the dihydro-oxazine *N*-oxide intermediate,[20] which could be diverted toward the formation of the cyclobutane intermediate[21] or subsequently to provide the nitroenamine intermediate **C**. Consequently, intramolecular Henry reaction of intermediate **C** via transition state **D** and protonation could yield nitroiminium **E** or **F**. Indeed, the formation of **5a** was also observed in the early stage of the reaction. The ratio of **5a**/**4a** was diminished as the reaction time increased, and **5a** was not observed after 8 days.[22] The preferential formation of **F** was probably due to the protonation of the nitroenamine intermediate, which favored attack from the convex face of the *cis*-indan system. As the reaction time was prolonged, with the assistance of prolinol catalyst **III**, **5a** was isomerized to the more stable **4a**.[23] The remarkable stereoselectivity of the cascade reaction may arise from two synergistic effects: (1) the severe steric hindrance caused by the bulky substituent at the catalyst (**TS B**), which directed the stereoselectivity of the reaction toward the dihydro-oxazine *N*-oxide intermediate, and (2) the interaction of the alcohol group on the prolinol catalyst with the dione through H-bonding activation, which not only helped in directing the stereoselectivity but also could drive the sluggish reaction toward product.

On the other hand, the reaction of cinnamaldehyde (**2b**), nitrostyrene **3a**, and 2-methylcyclopentane-1,3-dione (**1a**) with 20 mol % of diphenylprolinol (**III**) in H_2O–CH_3CN (2:1) at ambient temperature was slow, requiring a much longer time for the completion of the reaction (15 days). Instead of the expected product **4k**, the reaction afforded 39% yield of product **6**, which had a different chemoselectivity than **4**,[24,25] along with 35% yield of starting **3a** (60% yield of **6**, based on recovered starting material) and in only 13% ee (Figure 2).[26,27] The structure of



6 4k 7

Figure 2. Other derivatives.

adduct **6** was unambiguously characterized by X-ray diffraction of its single crystal (Figure 1). Alternatively, the reaction of acrolein **2a**, nitrostyrene **3a**, and 2-methylcyclohexane-1,3-dione (**1b**) with 20 mol % of diphenylprolinol (**III**) in H_2O–CH_3CN (2:1) at ambient temperature for 16 days gave 62% yield of adduct **7** (Figure 2) with 64% ee.[28] The structure of the adduct **7** was confirmed by X-ray structural analysis (Figure 1).

In summary, we have developed an organocatalytic and enantioselective multicomponent reaction of 2-methylcyclopentane-1,3-dione, nitroalkene, and α,β-unsaturated aldehyde with the diphenylprolinol catalyst to give highly functionalized Hajos–Parrish-type ketones with five to six contiguous stereocenters and two quaternary carbon stereogenic centers with high diastereoselectivity and enantioselectivity. The one-pot method not only provides a succinct process which adds to the arsenal of the HPESW reaction and highly functionalized HPK derivatives but also demonstrates an example of aqueous organocatalytic cascade reactions with cyclopentadione that are otherwise unprecedented. The structures of the appropriate products were unambiguously confirmed by single-crystal X-ray crystallographic analyses. Given the wide application of HPK compounds in synthetic and medicinal chemistry, this efficient cascade reaction method could constitute a valuable contribution with broad applications in chemical synthesis. Further utilization of this protocol in the synthesis of elaborated natural products is now in progress.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00459.

Experimental procedures and characterization data for the new compounds (PDF)
X-ray crystallographic data for compound (+)-**4a** (CIF)
X-ray crystallographic data for compound (+)-**4d** (CIF)
X-ray crystallographic data for compound (±)-**6** (CIF)
X-ray crystallographic data for compound (±)-**7** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) For recent reviews, see: Hong, B.-C.; Raja, A.; Sheth, V. M. *Synthesis* **2015**, *47*, 3257.

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(14) Intermediate **A** (shown in Table 1) is somewhat unstable for long-term storage. In addition, reaction of **A** with reagents in most organic solvents, giving back to **1a** and the chemically labile acrolein (via retro-Michael reaction), as well as the intramolecular Aldol product. For examples, see ref 9d and: Schick, H.; Roatsch, B.; Schwarz, H.; Hauser, A.; Schwarz, S. *Liebigs Ann. Chem.* **1992**, *1992*, 419.

(15) Organocatalysis reactions have been reported to be accelerated under the conditions of "on water". However, performing the reaction in organic solvent with a plethora of water would slow the reaction due to the hydrolysis of the initially formed enamine (reverse reaction). For recent examples of the organocatalysis "on water", see: (a) Bae, H. Y.; Song, C. E. *ACS Catal.* **2015**, *5*, 3613. (b) Hong, B.-C.; Kotame, P.; Liao, J.-H. *Org. Biomol. Chem.* **2011**, *9*, 382.

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(17) Without the presence of water, even the first Michael reaction of **1a** and **2a** did not proceed.

(18) The reaction was completed in ca. 36 h to give **4a** and its isomer **5a** (Scheme 3), and the rest of the time was required for the complete isomerization of **5a** to **4a**.

(19) For a Houk-like model, for the related model, see: Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.

(20) For the mechanistic studies on the reactions of aldehyde with nitroalkenes, catalyzed by diphenylprolinol silyl ether, see: (a) Seebach, D.; Sun, X.; Ebert, M.-O.; Schweizer, W. B.; Purkayastha, M.; Beck, A. K.; Duschmalé, J.; Wennemers, H.; Mukaiyama, T.; Benohoud, M.; Hayashi, Y.; Reiher, M. *Helv. Chim. Acta* **2013**, *96*, 799. (b) Seebach, D.; Sun, X.; Sparr, C.; Ebert, M.-O.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2012**, *95*, 1064. (c) Sahoo, G.; Rahaman, H.; Madarász, Á.; Pápai, I.; Melarto, M.; Valkonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13144.

(21) The cyclobutane was considered to be a parasitic component, an off-cycle resting state of the catalytic cycle; see ref 20.

(22) With the internal standard of 1,3,5-trimethoxybenzene, the ratio of **5a**/**4a** was found to be 72:28 (1 d, ~74% conversion), 33:67 (2 d), 21:79 (3 d), 10:90 (4 d), 7:93 (5 d), 5:95 (6 d), 3:97 (7 d), ~0:>99 (8 d).

(23) DFT calculation revealed that **4a** was more stable than **5a** by 1.81 kcal/mol, calculated by the Spartan'14 program, and the energies were obtained at the B3LYP/6-31G* level in water.

(24) Although the conversion is slow, adduct **6** was the only observable diastereomer in the crude ^{1}H NMR analysis.

(25) Interestingly, **1a** first reacted with nitrostyrene **3a** prior to cinnamaldehyde **2b**. It had a different chemoselective mode than the aforemention reaction of its α,β-unsaturated aldehyde counterpart, **2a**.

(26) It is interesting that **6** displayed a substructure that is reminiscent of that described by Enders and co-workers, who pioneered a triple cascade organocatalytic reaction of aldehyde, nitrostyrene, and α,β-unsaturated aldehyde, affording the cyclohexene carbaldehyde with four stereocenters; see: Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.

(27) Albeit in low enantioselectivity, the major absolute configuration of **6** was assigned as depicted on the basis of the observed VCD spectra and quantum chemical calculations of the corresponding spectra.

(28) Similarily, it has been reported that the intramolecular cyclization of the 2-(3-oxobutyl)cyclopentane-1,3-dione to Hajos–Parrish ketone afforded superior ee values compared to those reactions of 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione in the synthesis of the Wieland–Miescher ketone (93% ee vs 71% ee); see Scheme 1, refs 2 and 3, and: Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.

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