Brønsted Base-Catalyzed Domino Annulation of α-oxo-β, γ-Unsaturated Ketones and Malononitrile: Facile Access to Poly-substituted Tetrahydrocyclopenta[b]furanols

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Abstract: An efficient and atom-economical Brϕnsted base-catalyzed domino reaction of *α*-oxo-*β*, *γ*-unsaturated ketone is described. Under the catalysis of 20 mol% K_2CO_3, both symmetrical cinnamils and unsymmetrical *β*, *γ*-unsaturated diketones can react with malononitrile to produce polysubstituted tetrahydrocyclopenta[*b*]furanols in good to high yields and excellent diastereoselectivity. Three quaternary carbon centers and one tertiary carbon center can be constructed simultaneously, and the reaction can be easily scaled up.

Introduction:

Tetrahydrocyclopenta[*b*]furanols and their derivatives are a privileged fused heterocyclic skeletons frequently found in many natural products and

biologically active molecules, such as heliconol A-C,[1] HIV-1 protease inhibitors,[2] methyl rocaglate and rocaglamide,[3] PRMT5 inhibitors,[4] silvestrol and episilvestrol,[5] and so on[6] (Figure 1). These compounds exhibit a broad spectrum of important biological activities, including antifungal, anticancer, anti-inflammatory, anti-HIV and serine hydrolase inhibitory activities.

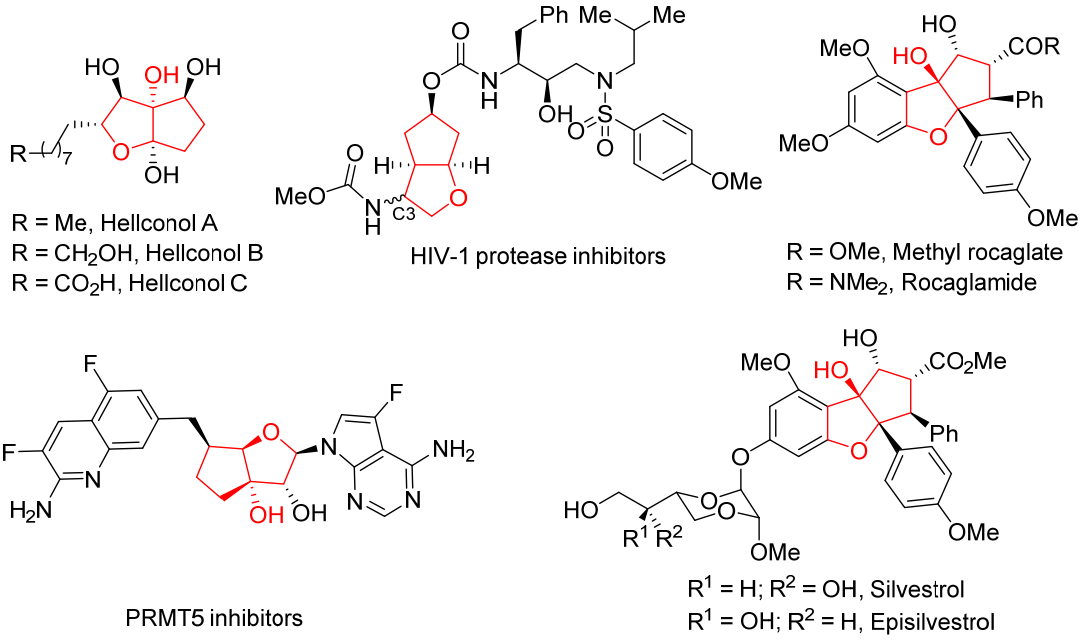
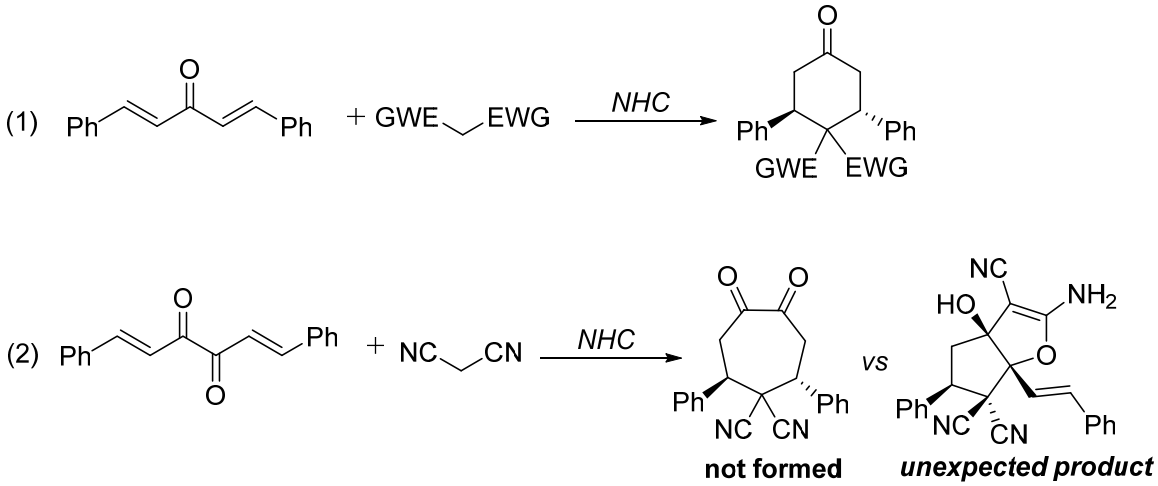


Figure 1 Representative bioactive tetrahydrocyclopenta[*b*]furanol derivatives

Despite the significance of tetrahydrocyclopenta[b]furanols, efficient method for the construction of these frameworks has been rarely developed. The domino reactions of *α*-oxo-*β*, *γ*-unsaturated carbonyls provide a powerful strategy for the synthesis of cyclic compounds. Based on the transformation of these building blocks, chemists prepared a large number of pharmaceutically active heterocycles and carbocycles, including

isoxazoles,[7] carbazoles,[8] pyridines,[9] furan derivatives,[10] pyran derivatives,[11] *β*-lactones,[12ab] butenolides,[12c] 9*H*-pyrrolo[1,2-a] indoles,[13] vinyl fulvenes,[14] cyclopentenones,[15] and so on.[16] We have been interested in the synthesis of polycyclic compounds[17] and found that N-heterocyclic carbene can catalyze double Michael-additions of active methylene compounds with dienones to form cyclohexanone derivatives (Scheme 1, eq.1).[17e-g] However, when 1,6-diphenylhexa-1,5-diene-3,4-dione (cinnamil) was used instead of dienone for the reaction, the desired cycloheptane-1,2-dione was not formed, and an unexpected tetrahydrocyclopenta[*b*]furanol was produced as the only product (Scheme 1, eq.2). Herein, we would like to report this interesting result.



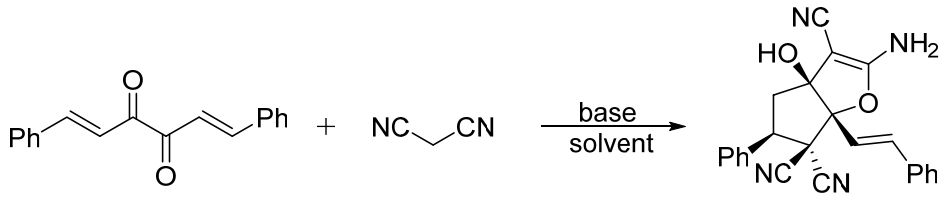
Scheme 1 Different annulation reactions of dienones and cinnamil

Results and Discussion：

Initially, the domino annulation reaction of cinnamil **1a** and malonodinitrile **2a** were selected as the model substrates to optimize the

reaction conditions (Table 1). With 10 mol% stable N-heterocyclic carbene (IPr, 1,3-bis(2,6-diisopropyl phenyl)-imidazole-2-ylidene)[18] as a Brønsted base, the domino reaction proceeded smoothly in THF at room temperature to afford the desired product **3a** in 77% yield and >20:1 d.r. within 10 min (Table 1, entry 1). Encouraged by this result, several other common organic bases, such as triethylamine, DBU, DABCO and DACH were examined for the reaction (Table 1, entries 2-5). All these bases can catalyze the domino annulation reaction to give the desired product in high yields. The strong inorganic base sodium hydroxide was also tested for the reaction, but only gave **3a** in low yield (Table 1, entry 6). Carbonate salts Na_2CO_3 and Cs_2CO_3 catalyzed the reaction in good yields (Table 1, entries 7 and 8). K_2CO_3 catalyzed the domino reaction to produce the desired product in the 96% yield (Table 1, entry 9). K_3PO_4 can also catalyze the reaction to afford **3a** in 92% yield (Table 1, entry 10). A brief screening of the reaction media showed that methanol was the best choice in terms of reaction yield (Table 1, entries 11-15). Lowering the base loading to 10 mol% resulted in decreased reaction yield (Table 1, entry 16). Finally, control experiment showed that in the absence of a base, no desired product was produced (Table 1, entry 17).

Table 1 Optimization of Reaction Conditions [a]



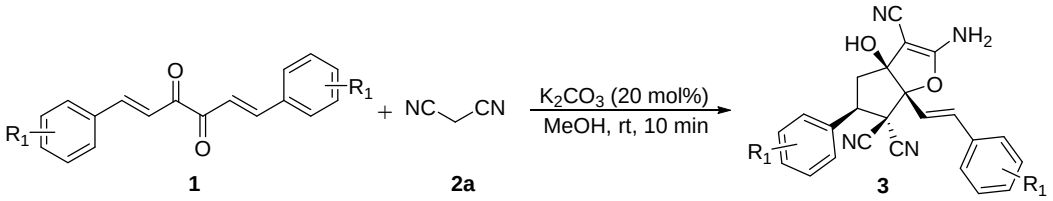
1a **2a** **3a**

entry	base	solvent	time (min)	yield (%)[b]	*d.r.*[c]
1	IPr	MeOH	1.5 h	77	> 20:1
2	Et_3N	THF	10	81	> 20:1
3	DBU	MeOH	10	85	> 20:1
4	DABCO	THF	10	83	> 20:1
5	DACH [d]	MeOH	1.5 h	88	> 20:1
6	NaOH	THF	10	60	> 20:1
7	Na_2CO_3	THF	1 h	83	> 20:1
8	Cs_2CO_3	THF	1.5 h	79	> 20:1
9	K_2CO_3	THF	20	96	> 20:1
10	K_3PO_4	THF	10	92	> 20:1
11	K_2CO_3	MeOH	2.5	99	> 20:1
12	K_2CO_3	CH_3CN	2 h	81	> 20:1
13	K_2CO_3	DMF	30	89	> 20:1
14	K_2CO_3	toluene	10	86	> 20:1
15	K_2CO_3	DCM	8 h	80	> 20:1
16 [e]	K_2CO_3	THF	2.5 h	82	> 20:1
17	no base	MeOH	10	/	/

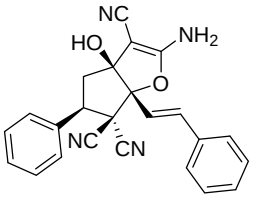
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), base (20 mol %), solvent (1.0 mL), rt; [b] isolated yield; [c] *dr* was determined via crude ^{1}H NMR spectra; [d] DACH: 1,2-diaminocyclohexane; [e] K_2CO_3 (10 mol %) was used.

Under the optimized reaction conditions, the generality and limitations of this method was then evaluated by reacting of various cinnamil**s** and malonodinitrile. As shown in Scheme 2, both electron-donating and electron-withdrawing groups substituted cinnamils participated in the domino annulation reaction smoothly to furnish the corresponding products in good to excellent yields (**3b**-**3j**). The steric effect was observed by checking of substrates with methyl group at different positions on the phenyl rings (**3b**-**3d**). 2-Naphthyl substituted cinnamil performed the reaction to give **3k** in 57% yield. We attributed this reduced yield to the steric effect of the bulky naphthyl groups. Substrates containing heteroaryl substituents such as 2-furyl and 2-thienyl were well tolerated, delivering the corresponding products **3l** and **3m** in high yields. The structure of **3a** was confirmed unambiguously by X-ray crystallographic analysis,[19a] which showed that the hydroxyl group, the phenyl group and the styryl group adopt a *cis* conformation.

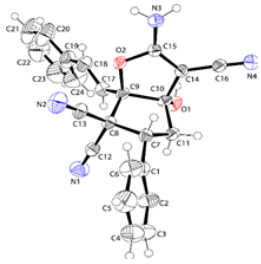
Scheme 2 Scope of cinnamils [a]



1 **2a** **3**



3a, 95%



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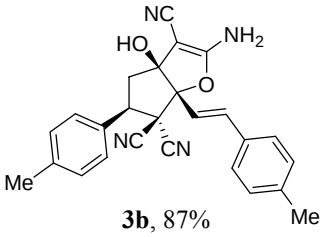
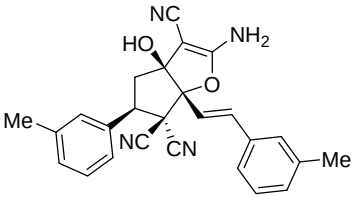
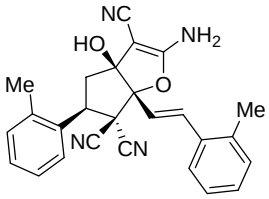


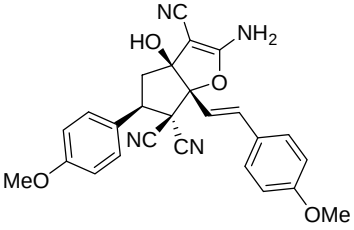
3b, 87%



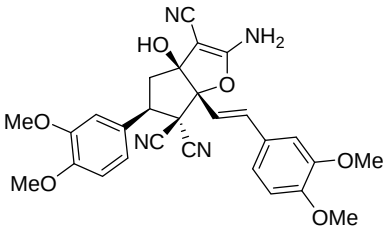
3c, 80%



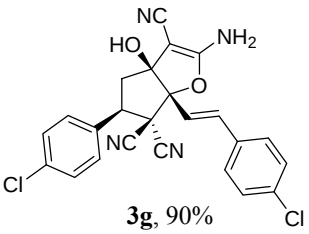
3d, 74%



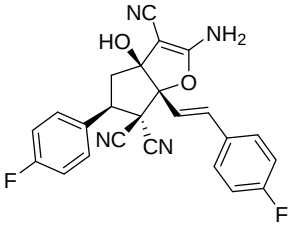
3e, 67%



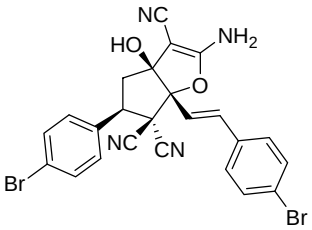
3f, 75%



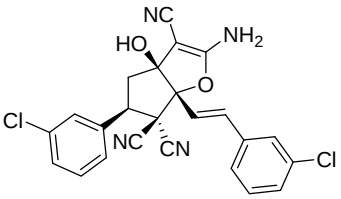
3g, 90%



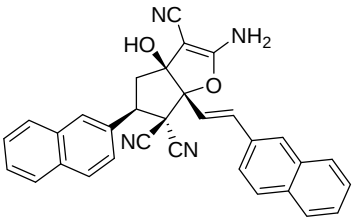
3h, 88%



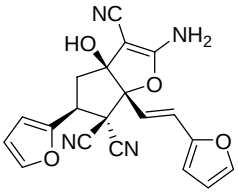
3i, 83%



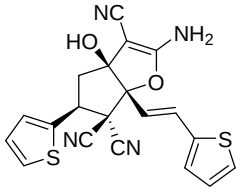
3j, 76%



3k, 57%



3l, 87%



3m, 90%

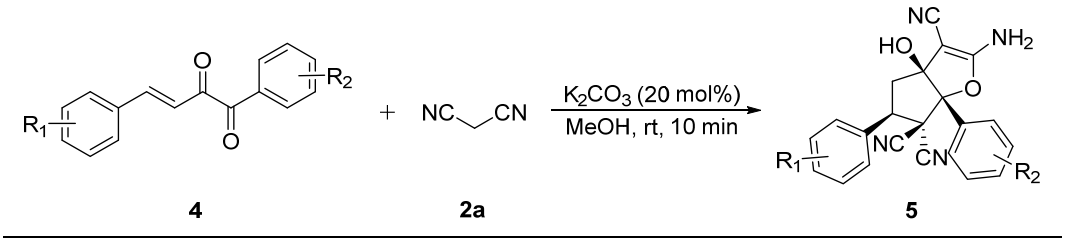
[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.3 mmol), K_2CO_3 (20 mol %), MeOH (1.0 mL), 10 min, rt; isolated yield; all *dr* > 20:1, which was

determined via crude ^{1}H NMR spectra.

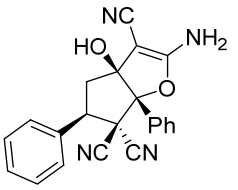
We next examined the reactivity of unsymmetrical *α*-oxo-*β*, *γ*-unsaturated ketones for this domino annulation reaction, and the results were summarized in Scheme 3. A variety of unsymmetrical *α*-oxo-*β*, *γ*-unsaturated ketones containing different substituents on phenyl rings could undergo the reaction and furnish the corresponding products **5a**-**5o** in moderate to excellent yields and >20:1 *dr* values. Substrates with either electron-donating, -neutral and -withdrawing groups at the *para*- position of the phenyl rings, including methyl, methoxyl, phenyl and chlorine, were well tolerated under the optimized reaction conditions, affording the corresponding tetrahydrocyclopenta[*b*]furanols in excellent yields (**5b**-**5f**). Exceptionally, *para*-bromo-substituted **4g** underwent the reaction to give **5g** in 62% yield. In addition, the steric effect was clearly demonstrated for substrates with substituents at *para*-, *meta*- or *ortho*- position of phenyl rings. As a result, the corresponding products were obtained in reduced yields in turn (**5b, 5h, 5i** and **5c, 5j, 5k**). When substrate **4l** was checked, the product **5l** was obtained in lower yield compared to mono-methoxy substituted substrates. We concluded that two electron-donating methoxyl groups lowered the reactivity of *α*-oxo-*β*, *γ*-unsaturated ketone **4l** dramatically and led to low reaction yield. Owing to the synergistic effects of steric repulsion and electron-donation, the bulky 2-naphthyl substituted *α*-oxo-*β*, *γ*-unsaturated ketone **4m** performed the reaction in low efficiency,

providing **5m** in 55% yield. Heteroaryl derived *α*-oxo-*β*, *γ*-unsaturated ketones underwent the reaction to furnish the corresponding products **5n** and **5o** in 56% and 63% yields, respectively. This result once again indicated that the electronic effects have obvious influence on the reactions. The relative configuration of the major diastereomer of **5a** was determined by X-ray crystallographic analysis.[19b]

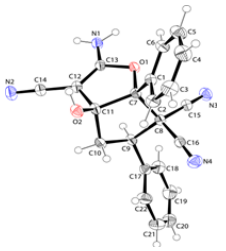
Scheme 3 Scope of unsymmetrical *α*-oxo-*β*, *γ*-unsaturated ketones [a]



4 **2a** **5**



5a, 96%



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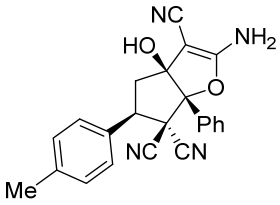
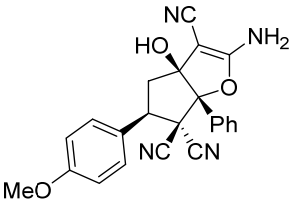
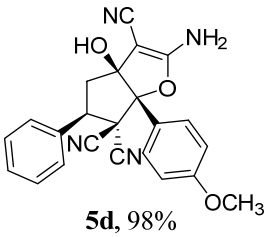


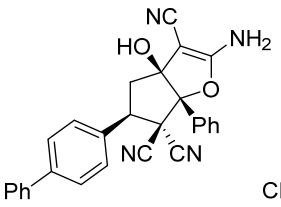
5b, 90%



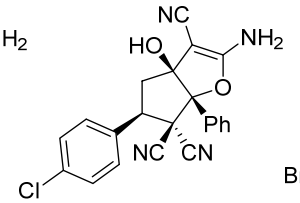
5c, 90%



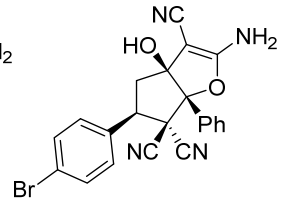
5d, 98%



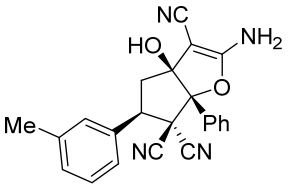
5e, 90%



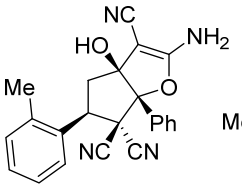
5f, 85%



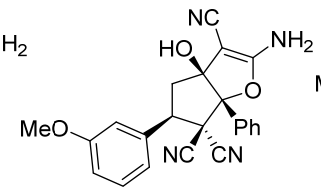
5g, 62%



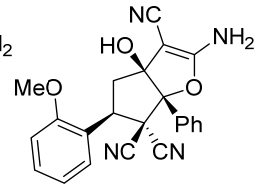
5h, 74%



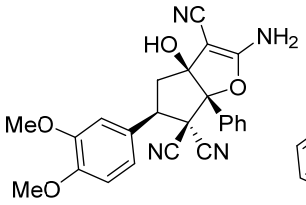
5i, 46%



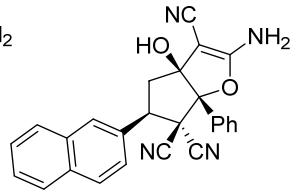
5j, 81%



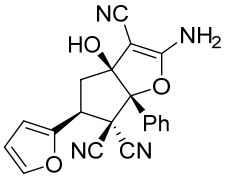
5k, 60%



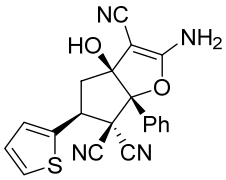
5l, 55%



5m, 55%



5n, 63%



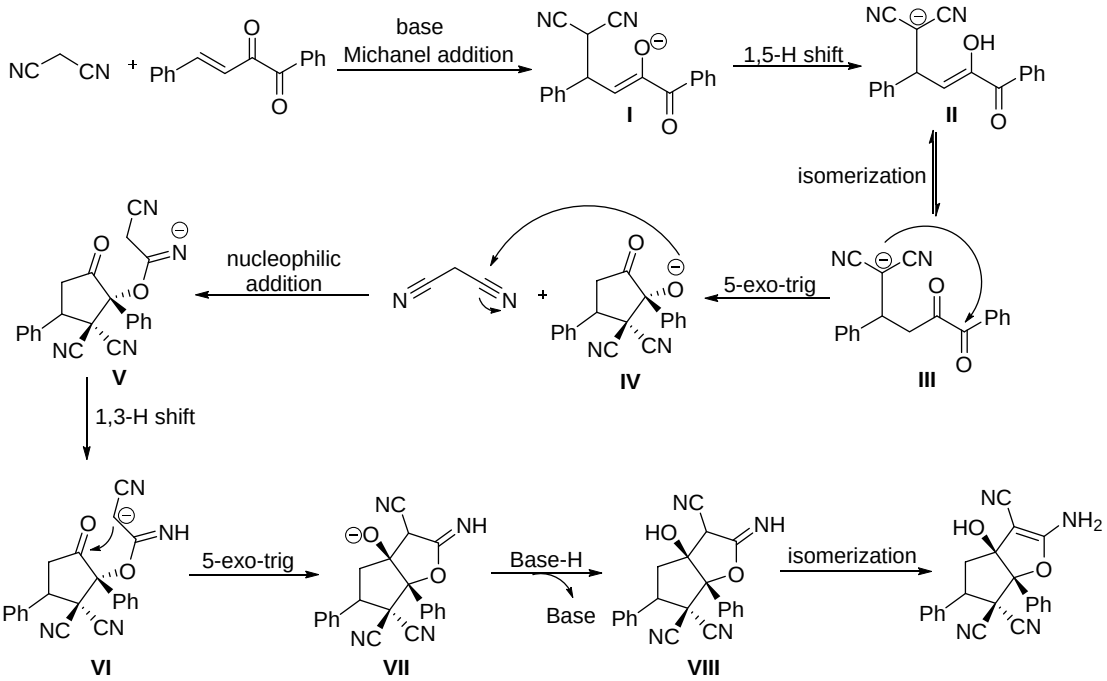
5o, 56%

[a] Reaction conditions: **4** (0.1 mmol), **2a** (0.3 mmol), K_2CO_3 (20 mol %), MeOH (1.0 mL), 10 min, rt; isolated yield; all *dr* > 20:1, which were determined via crude ^{1}H NMR spectra.

Based on previous reports on diastereoselective domino annulation involving alkenyl *α*-diketones or malononitrile, a tentative catalytic

mechanism was depicted in Scheme 4. Firstly, the deprotonation of malononitrile by brønsted base attacks the alkenyl 1,2-diketone generating intermediate **I**, which undergoes 1,5-H shift followed by isomerization affording intermediate **III**. Subsequently, 5-exo-trig annulation of intermediate **III** is happened to construct the poly-substituted 2-hydroxylcyclopentanone anion **IV**, which attacks the second molecule malononitrile resulting in intermediate **V**. After 1,3-H shift of intermediate **V** followed by intramolecular ring-closing, the intermediate **VII** is generated which protonated from conjugate acid of brønsted base giving intermediate **VIII** and along with regeneration of catalyst. Finally, after isomerization of intermediate **VIII**, the target product is obtained.

Scheme 4 Tentative Mechanism



Conclusions:

In conclusion, we have developed a domino annulation reaction of α-oxo-β, γ-unsaturated ketones and malononitrile. The transition-metal free and extremely mild conditions, very short reaction time, simple procedure and excellent diastereoselectivity provide a novel and practical method for rapid assemble of polysubstituted tetrahydrocyclopenta[*b*]furanols. Further studies on the detailed mechanism and the application of this method are currently underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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Notes and References

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19. CCDC 2074758 (**3a**) and 2074675 (**5a**) contain the supplementary crystallographic data for this paper. These data are available free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.