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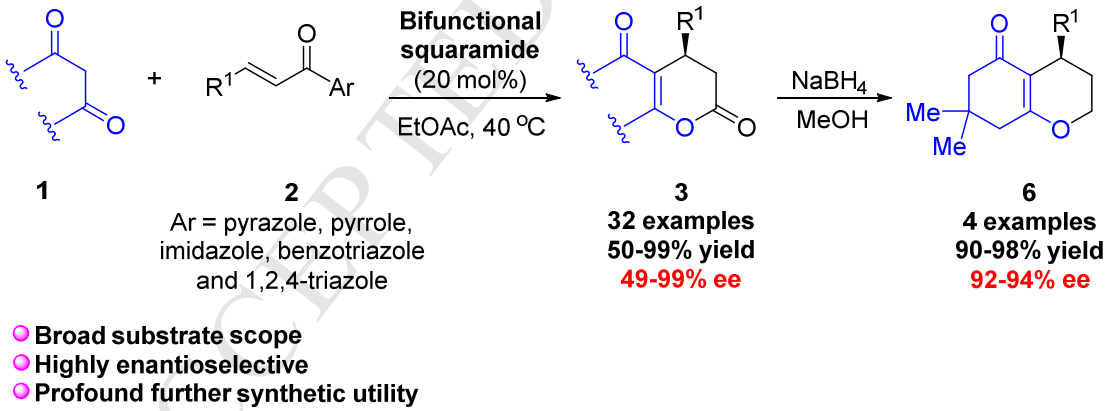

Enantioselective synthesis of fused dihydropyranones *via* squaramide-catalyzed Michael addition/lactonization cascade reaction

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Abstract: A highly enantioselective (49-99% ee) Michael addition/lactonization cascade process has been developed to construct 3,4-dihydropyran-2-one in the presence of a bifunctional squaramide. Various α,β-unsaturated *N*-acyl heterocycles were well tolerated and afforded 3,4-dihydropyran-2-ones in moderate to excellent isolated yields (50-99%). Both cyclic and acyclic β-diketones functioned as appropriate donors. The resulting 3,4-dihydropyran-2-ones could be readily converted into oxadecalinones.

Key words: dihydropyranone, α,β-unsaturated *N*-acylpyrazole, β-diketone, Michael addition, cascade reaction.

1. Introduction

3,4-Dihydropyran-2-one, also known as enol *δ*-lactone, is a class of privileged structural scaffold widely distributed in biologically active natural products and enormous pharmaceuticals.[1] The *cis*-3-aminohexahydrocoumarin derivatives **A** (Fig. 1), possessing an electron-deficient aromatic group or a heteroaromatic ring at the 4-position, displayed more powerful cytotoxicity to SW1116 cells with lower viability rates, when compared with doxorubicin hydrochloride, a potent

anti-cancer drug.[2] Meanwhile, these compounds also exhibited moderate to strong toxicity to SGC7901 cells.[2] In spite of interesting biological activities, 3,4-dihydropyran-2-ones have attracted intensive attention due to appealing synthetic perspective. The compounds of this type emerged as the crucial building blocks for the synthesis of a number of natural products. In this context, elaboration of dihydropyranone **B** (Fig. 1) allowed the total synthesis of (–)-7-deoxyloganin to be achieved in four subsequent steps.[3] In addition, 3,4-dihydro-2-pyranones have been recognized as the versatile precursors for the construction of pyridones, γ-lactones, benzenoid derivatives, *etc*.[1]

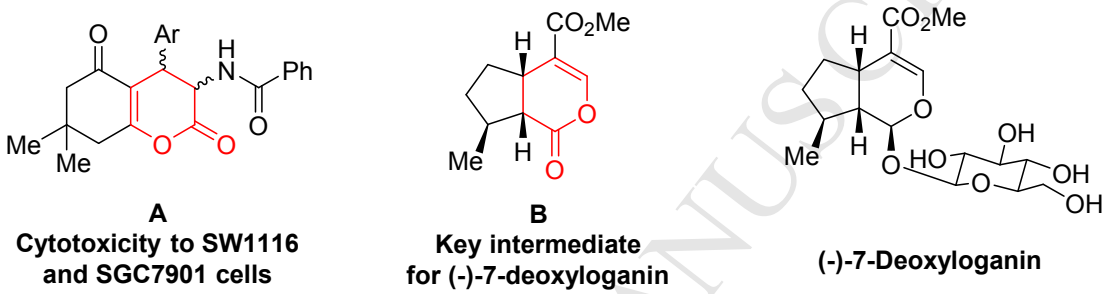


Fig. 1. Structurally important 3,4-dihydropyran-2-ones and natural product.

Given the inherent structural importance and attractive biological activity, great effort has been made to effectively access 3,4-dihydro-2-pyranones,[4] especially in an enantioselective fashion[2b,5]. Among all established synthetic approaches, the tandem Michael addition/lactonization process between 1,3-dicarbonyl compounds or enolate equivalent and α,β-unsaturated carbonyl compounds is one of the most concise and efficient methods to construct the 3,4-dihydropyran-2-one framework and represents the main preparative pathway. In this context, *N*-heterocyclic carbene (NHC) has played a particular active role in this field among all utilized catalysts.[1] A variety of 3,4-dihydro-2-pyranones were smoothly generated in a highly enantioenriched manner, using α,β-unsaturated acylazolium ions[6] or azolium enol/enolates[7] as the crucial reactive intermediates. As for all the often-used acceptors, α,β-unsaturated carboxylic acid derivatives remain a type of challenging substrate for the titled domino process.[8] In this regard, α,β-unsaturated pyrazolamides have been successfully employed by Kanemasa group to access enol *δ*-lactones with high levels of enantiopurities under double catalytic condition.[5a] However, in addition to Nickel complex, an external base was required to initiate this domino sequence.

Moreover, stoichiometric acetic anhydride was essential to prevent the formation of by-product. Unsaturated *N*-acylthiazolidinethiones were employed by Evans group to construct dihydropyranones in a stepwise manner.[5b] After the initial Michael addition, additional base was required to promote the further annulation process as well. Moreover, Du[5e] and Albrecht[5i] have confirmed α,β-unsaturated *N*-acylated succinimides and β,γ-unsaturated-α-ketophosphonates to be competent partners for the tandem process of this type, respectively. However, the optical purities of the most products awaited further improvement. Therefore, further exploration of efficient catalytic method for the synthesis of enantioenriched enol *δ*-lactone *via* α,β-unsaturated carboxylic acid derivatives has become an urgent task.

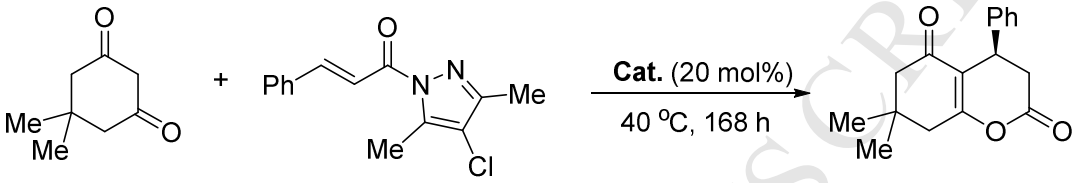
Based on our continuous effort on the asymmetric Michael addition involving α,β-unsaturated carboxylic acid derivatives,[9] herein we would like to present a highly enantioselective domino Michael addition/lactonization sequence mediated by a chiral squaramide. A wide range of cyclic or acyclic β-diketones smoothly reacted with α,β-unsaturated *N*-acylpyrazoles[10], delivering enol *δ*-lactones in high yields and excellent enantiomeric purities. Moreover, the reactivity of this cascade process depended closely on the electron-withdrawing character and leaving ability of the heterocycles besides carbonyl group within the context of the acceptor.

2. Result and discussion

We commenced with our investigation using dimedone **1a** and α,β-unsaturated pyrazolamide **2a** as the model substrates. Gratifyingly, the desired [3+3] annulation product **3aa** was smoothly obtained with promising enantioselectivity in the presence of quinine-based bifunctional thiourea **C1**,[11] albeit the reactivity awaited further improvement (Table 1, entry 1). Other cinchona alkaloid-derived thioureas **C2-C4** delivered enol *δ*-lactone with slightly poorer optical purity (entries 2-4 *vs* entry 1). We successively turned our attention to evaluate the effect of solvent. It was indicated that the reactivity of this domino process was correlated closely with the polarity of the solvent. In general, the reactivity increased as the polarity of the solvent increased with exception of acetonitrile (ACN) (entries 5-9). Among all solvent studied, ethyl acetate (EtOAc) emerged as the preferable one due to the superior reactivity and comparable enantioselectivity. Further optimization study disclosed that the bifunctional squaramide **C5** proved to be the favorable catalyst in terms of reactivity and enantiocontrol.[12] Notably, extending space between

the squaramide moiety and the aryl group embedded in the catalyst resulted in dramatically erosion of enantiomeric excess and reactivity (entry 11 *vs* entry 10).[12] Moreover, highest isolated yield was achieved when this formal [3+3] cycloaddition reaction was performed with a 2:1 ratio of donor **1a** to acceptor **2a**; either increasing or reducing the substrate ratio of **1a** to **2a** led to diminished reactivity (entries 12-14 *vs* entry 10).

Table 1 Optimization of reaction conditions.[a]



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

Entry	Cat.	Solvent	Yield (%) [b]	ee (%) [c]
1	**C1**	toluene	37	92
2	**C2**	toluene	44	82
3	**C3**	toluene	44	-87
4	**C4**	toluene	54	-87
5	**C1**	$PhCF_3$	76	86
6	**C1**	DCM	56	91
7	**C1**	THF	78	92
8	**C1**	EtOAc	91	87
9	**C1**	ACN	65	95
10	**C5**	EtOAc	90	97
11	**C6**	EtOAc	90	85
12[d]	**C5**	EtOAc	82	97
13[e]	**C5**	EtOAc	68	96
14[f]	**C5**	EtOAc	85	97

[a] Unless otherwise noted, the reactions were performed with 0.2 mmol of **1a**, 0.1 mmol of α,β-unsaturated pyrazolamide **2a**, 20 mol % of catalyst in 1 mL of solvent at 40 °C for 168 hours.

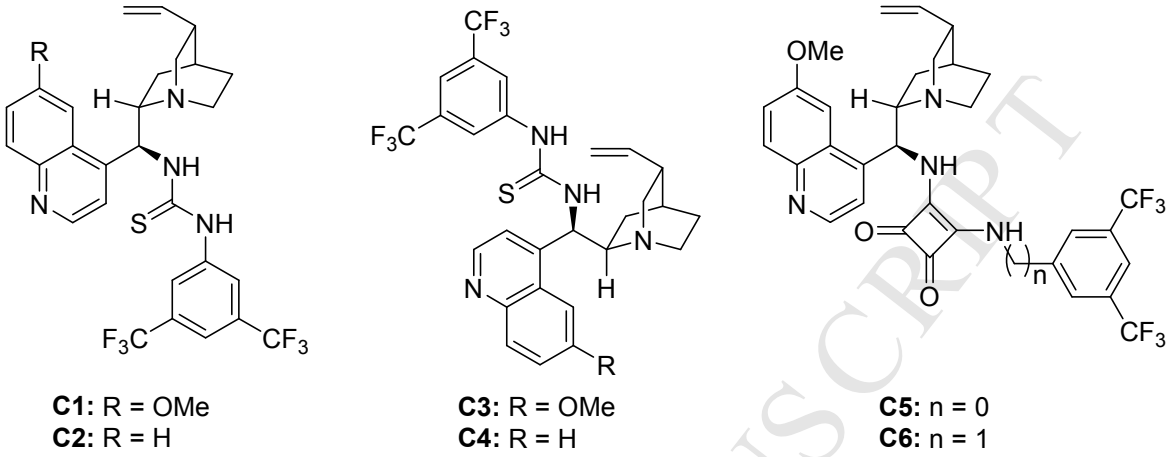
[b] Isolated yield after flash chromatography on silica gel.

[c] Determined by HPLC on chiral OJ-H column.

[d] Performed with 0.15 mmol of **1a**, 0.1 mmol of **2a**.

[e] Performed with 0.1 mmol of **1a**, 0.1 mmol of **2a**.

[f] Performed with 0.1 mmol of **1a**, 0.2 mmol of **2a**.



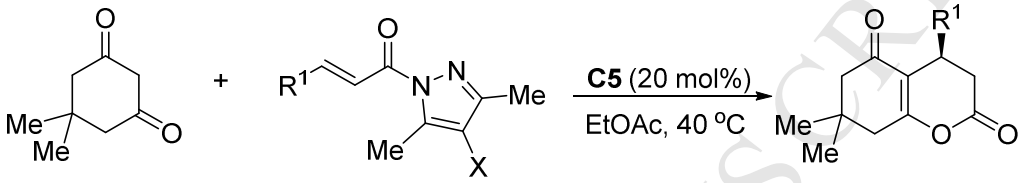
C1: R = OMe
C2: R = H
C3: R = OMe
C4: R = H
C5: n = 0
C6: n = 1

Fig. 2. The structure of bifunctional organocatalysts.

Once the optimal reaction condition was established, a range of various α,β-unsaturated pyrazolamides **2** were examined to explore the substrate generality of this protocol. As list in table 2, the Michael addition/lactonization sequence proceeded smoothly with a variety of chloride-substituted *N*-acylpyrazoles **2b**-**2j** of different electronic property in ethyl acetate at 40 ^{o}C promoted by 20 mol% of bifunctional squaramide **C5**, allowing access to the annulation products **3ab**-**3aj** with excellent enantiopurities (Table 2, 2-10). Generally, the electron-deficient acceptors **2c**, **2d**, **2f**-**2h** displayed slightly higher reactivity in comparison with electron-rich acceptors **2i** and **2j** (entries 3, 4, 6-8 *vs* entries 9 and 10). This tandem reaction was very sensitive to steric hindrance imposed by substituents on the phenyl group. Significant decrease of isolated yield was observed in the case of *ortho*-substituted substrates **2b** and **2e**, when compared with the corresponding *para*- and *meta*-substituted substrates (entry 2 *vs* entries 3 and 4, entry 5 *vs* entry 6). **2k**, possessing a bulky naphthyl group on the terminal of the double bond, was well tolerated by this catalytic system, giving dihydropyranone **3ak** in quantitative yield and 95% ee (entry 11). The heteroaromatic acceptor **2l** readily participated in this domino reaction, allowing access to **3al** with high degrees of optical purity (entry 12). In addition to chloride-substituted *N*-acylpyrazoles, bromide- and iodine-containing analogues **2m**-**2o** were suitable partners as well (entries 13-15). In particular, almost enantiomerically pure product **3am** was formed in the case of furyl-substituted

acceptor **2n**. Remarkably, halogen-free *N*-acylpyrazoles **2p** and **2q** were compatible with this cascade sequence, even exhibiting higher reactivities in contrast with the corresponding chloride-containing compounds **2a** and **2g** (entry 16 *vs* entry 1, entry 17 *vs* entry 7). The absolute configuration of the enol *δ*-lactone **3aa** was established as *S via* comparison of HPLC traces and optical rotation value with that of literatures reported,[5a,5e] other adducts were assigned by analogy.

Table 2 Substrate scope of α,β-unsaturated pyrazolamides.[a]



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

Entry	R_1/X (**2**)	**3**	Time (h)	Yield (%) [b]	ee (%) [c]
1	Ph/Cl (**2a**)	**3aa**	168	90	97
2	*o*-ClC_6H_4/Cl (**2b**)	**3ab**	168	53	96
3	*m*-ClC_6H_4/Cl (**2c**)	**3ac**	168	90	99
4	*p*-ClC_6H_4/Cl (**2d**)	**3ad**	168	90	96
5	*o*-BrC_6H_4/Cl (**2e**)	**3ae**	168	50	90
6	*p*-BrC_6H_4/Cl (**2f**)	**3af**	168	75	96
7	*p*-FC_6H_4/Cl (**2g**)	**3ag**	168	77	96
8	*p*-$CF_3C_6H_4$/Cl (**2h**)	**3ah**	168	85	97
9	*p*-MeC_6H_4/Cl (**2i**)	**3ai**	168	73	98
10	*p*-$MeOC_6H_4$/Cl (**2j**)	**3aj**	168	80	93
11	2-naphthyl/Cl (**2k**)	**3ak**	120	99	95
12	2-thienyl/Cl (**2l**)	**3al**	168	94	97
13	Ph/Br (**2m**)	**3aa**	144	99	96
14	2-furyl/Br (**2n**)	**3am**	168	94	99
15	Ph/I (**2o**)	**3aa**	168	90	96
16	Ph/H (**2p**)	**3aa**	120	99	96
17	*p*-FC_6H_4/H (**2q**)	**3ag**	168	79	96

[a] Unless otherwise noted, the reactions were performed with 0.2 mmol of **1a**, 0.1 mmol of α,β-unsaturated

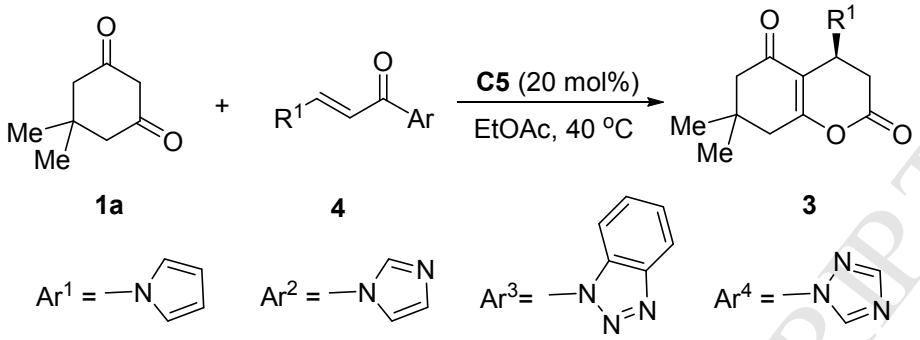
pyrazolamide **2**, 20 mol % of **C5** in 1 mL of EtOAc at 40 ^{o}C for due reaction time.

[b] Isolated yield after flash chromatography on silica gel.

[c] Determined by HPLC analysis on chiral stationary phases.

Having identified α,β-unsaturated *N*-acylpyrazole **2** as the appropriate counterpart, we subsequently explored the substrate scope of other cinnamic *N*-acyl heterocycles. To our delight, the titled cascade reaction worked well with a range of acceptors containing different heterocycles, including pyrrole (Ar^1),[13] imidazole (Ar^2),[14] benzotriazole (Ar^3)[15] and 1,2,4-triazole (Ar^4)[6k] (Table 3, entries 1-4). Generally speaking, the reactivity of these acceptors depended closely on electron-withdrawing character and leaving ability of the heteroaromatic residues beside the carbonyl groups (Fig. 3).[8] This domino reaction proceeded *via* the initial Michael addition and the following lactonization to afford the resulting enol *δ*-lactone. The rate of Michael addition depended strictly on the electron-withdrawing ability of the heterocyclic residue (Ar), whose enhancement lowered the lowest unoccupied molecular orbital (LUMO) energy and favored the conjugate addition. Meanwhile, the lactonization process correlated directly with the cleavage of amide-type C(O)-N bond. The cleavage easiness of heterocycle was a function of the anion stability, and therefore a rough measure was taken into account by the pKa value of the corresponding conjugated acid (ArH). As depicted in Figure 2, **4a** and **4b** were relatively poorer Michael acceptors. Moreover, the leaving ability of pyrrole and imidazole residues was inferior to benzotriazole and 1,2,4-triazole residues. As a result, cinnamic *N*-acyl pyrrole **4a** and cinnamic *N*-acyl imidazole **4b** furnished enol *δ*-lactone **3aa** just in moderate isolated yield even after 168 hours. In contrast, the domino reaction went to completion after 48 hours and provided the target product **3aa** in almost quantitative isolated yield in the case of **4c** and **4d**. Moreover, variation of heterocyclic substituents from pyrazoles to 1,2,4-triazles also gave rise to considerable enhancement of reactivity. Although those *N*-acyl pyrazoles, **2b**, **2e**-**2g**, **2i** and **2j** afforded unsatisfactory isolate yields even after 168 hours (Table 2, entries 2, 5-7, 9 and 10), complete conversions (90-99% yield) were detected for the corresponding *N*-acyl 1,2,4-triazoles **4e**-**4j** only after 48-72 hours (entries 5-10). Inspired by these encouraging results, the aliphatic substrate **4k** was also utilized and treated with dimedone **1a**, resulting in formation of **3an** in synthetically useful yield and prominent enantiomeric excess (entry 11).

Table 3 Substrate scope of *N*-acyl heterocycles. [a]



Entry	R_1/Ar (**4**)	**3**	Time (h)	Yield (%) [b]	ee (%)[c]
1	Ph/Ar^1 (**4a**)	**3aa**	168	54	94
2	Ph/Ar^2 (**4b**)	**3aa**	168	53	96
3	Ph/Ar^3 (**4c**)	**3aa**	48	99	94
4	Ph/Ar^4 (**4d**)	**3aa**	48	99	94
5	*o*-ClC_6H_4/Ar^4 (**4e**)	**3ab**	48	90	91
6	*o*-BrC_6H_4/Ar^4 (**4f**)	**3ae**	48	94	91
7	*p*-BrC_6H_4/Ar^4 (**4g**)	**3af**	48	94	92
8	*p*-FC_6H_4/Ar^4 (**4h**)	**3ag**	48	94	90
9	*p*-MeC_6H_4/Ar^4 (**4i**)	**3ai**	48	99	93
10	*p*-$MeOC_6H_4$/Ar^4 (**4j**)	**3aj**	72	90	92
11	Me/Ar^4 (**4k**)	**3an**	72	90	93

[a] Unless otherwise noted, the reactions were performed with 0.2 mmol of **1a**, 0.1 mmol of **4**, 20 mol% of **C5** in 1 mL of EtOAc at 40 °C for due reaction time.

[b] Isolated yield after flash chromatography on silica gel.

[c] Determined by HPLC on chiral OJ-H column.

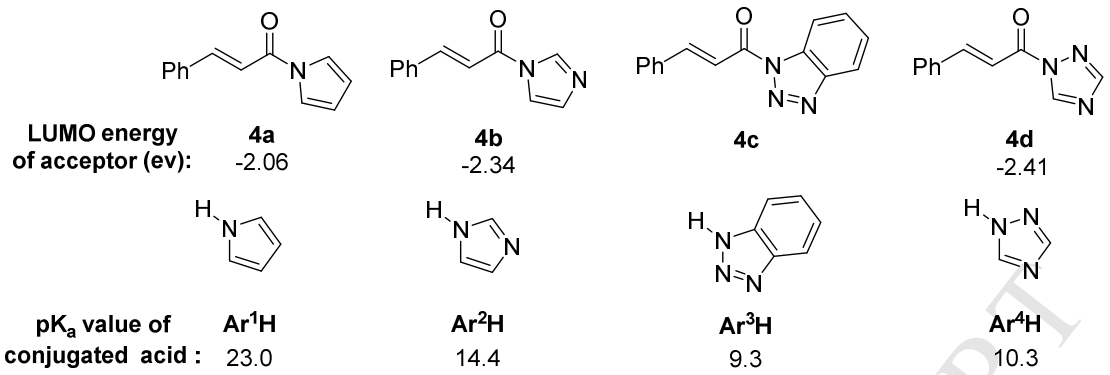
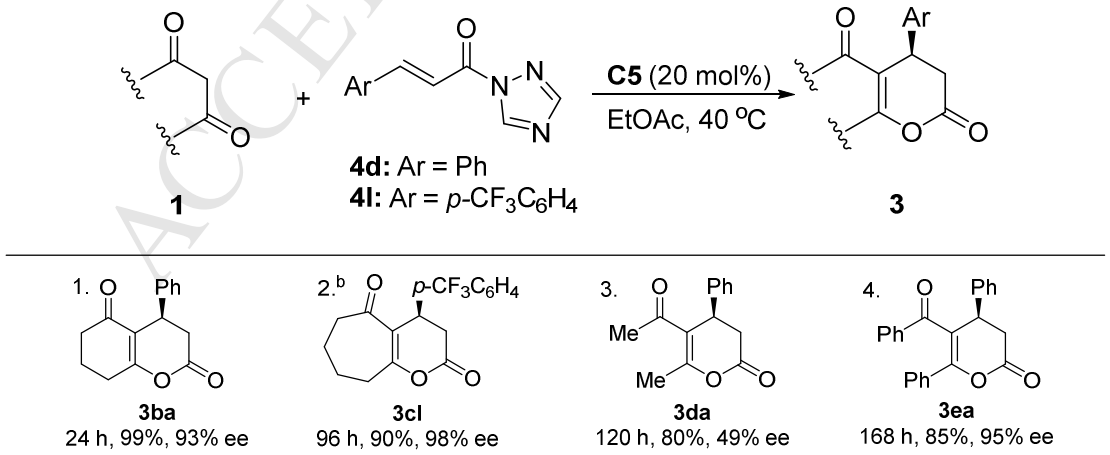


Fig. 3. The electron-withdrawing character and leaving ability of heterocycles.

Next, the substrate scope was also investigated with respect to β-diketones. 1,3-Cyclohexanedione even displayed higher reactivity than dimedone **1a** (Table 4, entry 1). Although 1,3-cyclopentadione was totally inert under the standard conditions, the seven-member analogue, 1,3-cycloheptanedione, allowed efficient formation of fused product **3cl** with 98% ee at elevated temperature (entry 2). Acyclic β-diketones were appropriate donors as well, but prolonged reaction time was required in contrast with cyclic ones (entries 3 and 4). Delightfully, excellent enantiopurities were obtained for these β-diketones except acetylacetone *via* our approach, albeit the pioneering study indicated that all these compounds were challenging donors owing to poor enantiocontrol.[5e]

Table 4 Substrate scope of 1,3-dicarbonyl compounds. [a]

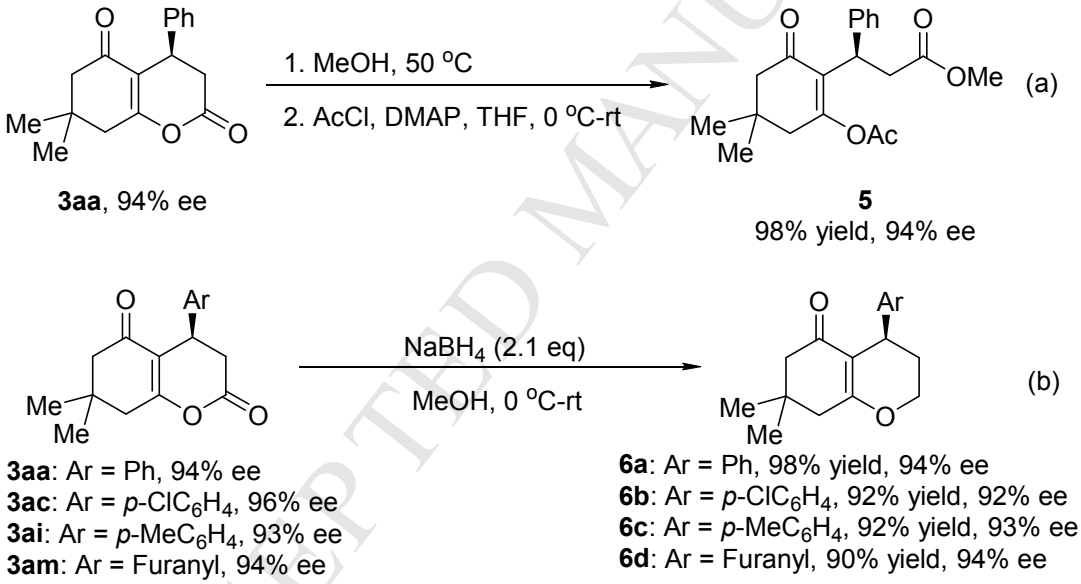


[a] Unless otherwise noted, the reactions were performed with 0.2 mmol of **1a**, 0.1 mmol of **4**, 20 mol% of **C5** in 1 mL of EtOAc at 40 °C for due reaction time. Isolated yield after flash chromatography on silica gel. The

enantioselectivity was determined by HPLC analysis on chiral stationary phases.

[b] Performed at 60 °C.

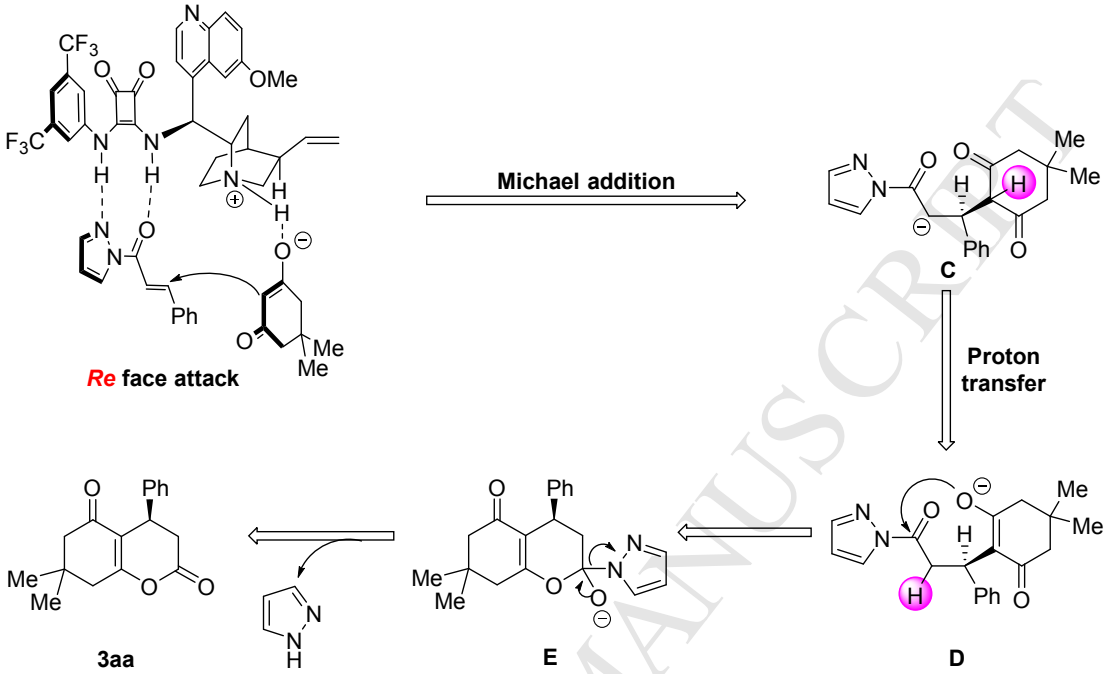
The enantioenriched dihydropyranones generated *via* this domino process are synthetically versatile materials. Alcoholysis of **3aa** and further protection as acetate occurred smoothly to afford product **5** in good yield without compromise of enantiopurity (Scheme 1, a). In addition, chemoselective reduction of ester motif worked properly with 2.1 equiv of sodium borohydride under mild reaction conditions (Scheme 1, b).[16] Although a slight loss of optical purity was observed in the case of **6b**, other dihydropyranones gave rise to the desired oxadecalinones[17] without detectable racemization. Notably, oxadecalinones are the core skeletons of many interesting natural products, including arisugacin A,[18] phomactin A[19] and orevactaene[20].



Scheme 1. Synthetic manipulations of dihydropyranone.

To account for the observed stereochemical outcome of this cascade reaction, a plausible transition state model was proposed and described in Scheme 2.[21] The squaramide moiety of catalyst **C5** was believed to form dual hydrogen-bondings with carbonyl group and nitrogen embedded in pyrazole motif, thereby increasing the electrophilicity of α,β-unsaturated pyrazolamide. Meanwhile, dimedone was deprotonated and orientated by the tertiary amine subunit of catalyst **C5**. Therefore, the Michael addition occurred *via* attack *Re*-face of acceptor. The following proton transfer proceeded within the conjugated addition intermediate **C**, giving

rise to the corresponding enolate anion **D**. This resulting enolate anion attacked the amide carbonyl group to afford cyclic intermediate **E**. The consequent C-N cleavage generated the desired dihydropyranone **3aa**, accompanied by the release of pyrazole.



Scheme 2. Proposed reaction pathway for the cascade sequence.

3. Conclusion

In conclusion, a highly enantioselective (49-99% ee) Michael addition/lactonization cascade process has been developed to construct 3,4-dihydropyran-2-one in the presence of a bifunctional squaramide. Various α,β-unsaturated *N*-acyl heterocycles were well tolerated and afforded 3,4-dihydropyran-2-ones in moderate to excellent isolated yields (50-99%). Both cyclic and acyclic β-diketones functioned as appropriate donors. The resulting 3,4-dihydropyran-2-ones could be readily converted into oxadecalinones. Moreover, a single squaramide was sufficient to accomplish this enantioselective transformation, and no additional additive was required in comparison with previous protocol.[5a,5b] The related domino reaction employing acceptor of this type is well underway in our lab.

Acknowledgements

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