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An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in Organocatalytic Multicomponent Reaction

Tushar M. Khopade, Trimbak B. Mete, Jyotsna S. Arora and Ramakrishna G. Bhat*

Abstract: Enantioselective organocatalytic multicomponent reaction of aldehyde, ketone and Meldrum's acid has been developed. Cinchona based primary amine (1 mol%) catalyzes the multicomponent reaction via the formation of Knoevenagel product and chiral enamine to form enantiopure *δ*-keto Meldrum's acids in a tandem catalytic pathway. An adverse effect of higher catalyst loading and longer reaction time on enantioselectivity is studied. This mild protocol provides an easy access to enantiopure carboxylic acids, esters and amides and the method proved to be scalable on a gram scale. DFT calculations were carried out on the proposed reaction mechanism and they were in close agreement with the experimental results.

Aminocatalysis is one of the essential pillars in the field of organocatalysis and is often explored in several complex multicomponent reactions.[1-3] At the dawn of asymmetric organocatalysis, various research groups independently discovered that the aminocatalysts possess an unprecedented strength of catalyzing a number of diverse multicomponent processes very efficiently and selectively to generate a broad array of diverse optically active compounds.[4] However, to identify a suitable catalyst and set of conditions is always crucial for the success of enantioselective multicomponent reactions. List and co-worker[5] reported an efficient proline-catalyzed three component Knoevenagel-Michael addition reaction of Meldrum's acid, aldehyde and ketone (see Fig 1 A). Although this elegant C-C bond forming reaction is highly diastereoselective, it lacks enantioselectivity. Furthermore, in addition to the desired reaction sequence, numerous pathways are possible which can compete by leading to the undesired products. For example, Barbas and co-worker[6] demonstrated a very same reaction that furnished four products when pyrrolidine was used as a catalyst (see Fig 1, B).

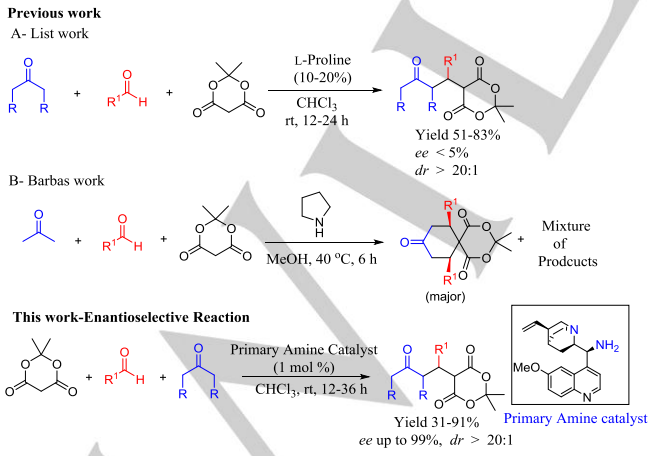
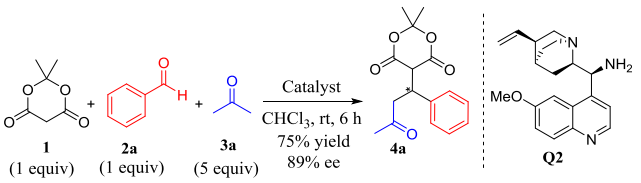


Figure 1. Multicomponent reaction of ketones, aldehydes and Meldrum's acid

To our surprise, this highly efficient C-C bond forming enantioselective three component process still remained an unmet challenge and this encouraged us to investigate an appropriate catalyst system for the same.

We believed that the modularly designed organocatalyst assembly developed by Zhao group[7] or cinchona based primary amine catalysts[3c] might overcome the ineffective enantiodiscrimination catalyzed by proline. In general, it is often assumed that reactions work smoothly when aminocatalysts are employed in the range of 10-30 mol%. However, their counterproductive effects on the chemoselectivity and stereoselectivity are rarely observed and studied.[8] To the best of our knowledge, the counterproductive effects of high-catalyst loading of aminocatalyst and longer reaction time in the multicomponent reactions are not observed till date. Herein, in this communication, we report the very first enantioselective organocatalytic multicomponent reaction of aldehyde, ketone and Meldrum's acid and the study on significant effect of low-catalyst loading on the enhancement in the enantioselectivity of multicomponent reaction.

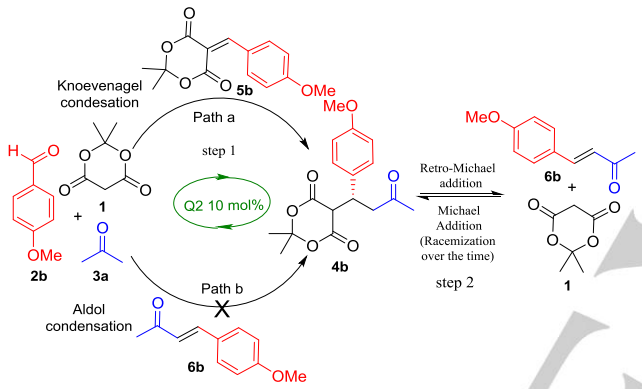
At the outset, we began our investigation by treating Meldrum's acid **1**, benzaldehyde **2a** and acetone **3a** with D-proline and various other catalyst modules (Scheme 1 and see ESI for the screening table). Initial screening with D-proline as well as modularly designed catalysts (D-proline/D-phenylglycine and chiral thiourea catalyst)[7] afforded the desired product **4a** with extremely poor enantioselectivity (4-5% *ee*). Hayashi-Jørgensen catalyst and other catalyst assemblies comprising of chiral thiourea and amino acids such as D-aspartic acid, D-glutamic acid, D-pipecolic acid led to unsatisfactory results. After exhaustive screening, we turned our attention towards cinchona based primary amine bi-functional catalyst **Q2**. Gratifyingly, quinine based bi-functional primary amine catalyst **Q2** (10 mol%) furnished the desired product **4a** in 75% yield with very good enantioselectivity (89 % *ee*) with considerably shorter reaction time at room temperature (6 h, rt, see ESI). After establishing the suitable catalyst system, further, the effect of solvents on enantioselectivity was examined (see ESI). Screening of various solvents revealed that chloroform is the best solvent for the desired transformation. Primary amine catalyst (**Q2**, 10 mol%) in chloroform at room temperature was established as optimized reaction conditions.



Scheme 1. Bifunctional amine catalyzed model reaction

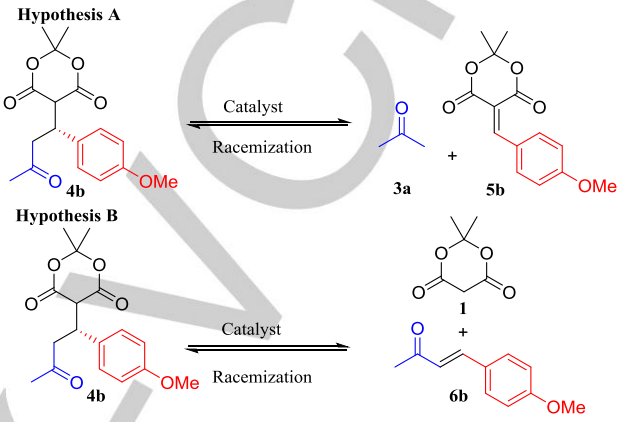
Having optimized the reaction conditions in hand, we planned to extend the scope of the reaction using various aldehydes and ketones for the generality of the protocol. Initially, the reaction of Meldrum's acid **1**, 4-methoxybenzaldehyde **2b** and acetone **3a**

under optimized reaction conditions afforded the corresponding product **4b** in 50% yield with 72% *ee* after 6 h. However, when we tried to increase the yield by stirring the reaction for an extended period of time, to our surprise, the enantioselectivity was drastically lowered from 72% *ee* at 6 h to 10% *ee* at 48 h. This unanticipated observation indicated the probable negative influence of longer reaction time on the enantioselectivity. In order to validate this finding, further, we repeated the same reaction and recorded the enantiomeric excess of the product **4b** at different time intervals as summarized in Figure 2 (black line). Surprisingly, we observed that the initial very good enantioselectivity (86% *ee* at 1.5 h) was found to be eroding continuously over a period of time and virtually became racemic after 72 h (Fig. 2, black line 10 mol% **Q2**). However, unlike **Q2** D-proline catalyzed reaction led to the racemic product in a short period of time (1 h). Prior to unravel the root cause of racemization over a period of time, it was important to understand the possible pathways of this transformation.



Scheme 2. Possible pathways for the product **4b**

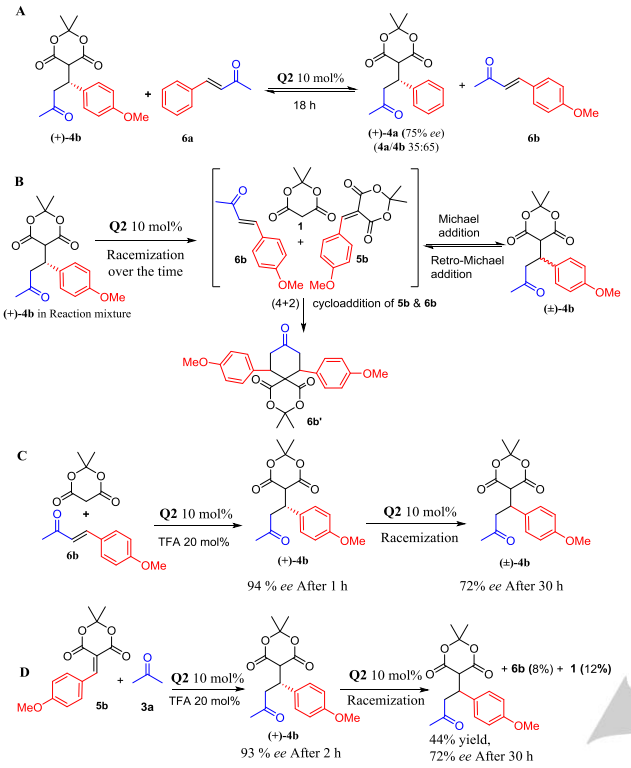
We firmly believed that three-component reaction of **1**, **2b** and **3a** can proceed via either Knoevenagel-Michael reaction pathway (path a) or Aldol-Michael reaction pathway (path b) (Scheme 2). In order to investigate the most plausible pathway, we carried out the time-dependent ^{1}H NMR experiments of the reaction mixture (see ESI for the stacked spectrum). It was very interesting to observe that an intense peak (s, 8.32 ppm) corresponding to alkylidene Meldrum's acid **5b** appeared immediately within 10 minutes. This peak disappeared over a period of time, while the characteristic peak (dd, 3.01 ppm) corresponding to the product **4b** intensified gradually over a period of time (10 min - 8 h). Likewise, the time-dependent ^{1}H NMR experiments of the reaction mixture of **4a** gave a similar pattern of results. However, interestingly we also noticed that initially absent or insignificant characteristic peaks corresponding to benzylidene acetone **6a** (d, 6.72 ppm) and 4-methoxybenzylidene acetone **6b** (d, 6.61 ppm) slowly appeared along with the product peak (see ESI). Based on this interesting observation we surmised that either the initially formed products **4a**/**4b** (via Knoevenagel-Michael pathway, path a) slowly underwent elimination of Meldrum's acid **1** thus leading to **6a**/**6b** or aldol condensation competed meekly with the path a. In order to validate further, we carried out the reaction of 4-methoxybenzaldehyde **2b** and acetone **3a** in the presence of catalyst **Q2** (10 mol%). Interestingly, the anticipated aldol condensation product **6b** (*p*-methoxybenzylidene acetone) was not obtained. Surprisingly, 20 mol% of Meldrum's acid **1** along with **Q2** (10 mol%) catalyzed the formation of **6b** in trace amount (see ESI eq. 2, S23). These findings unambiguously infer that the reaction is proceeding via Knoevenagel-Michael reaction pathway (path a).



Scheme 3. Possible routes for the racemization

Further, in the quest for finding the reason for the erosion in enantioselectivity over a period of time we conceived two probable hypotheses A and B (Scheme 3). In both the hypotheses, enantiopure compound **4b** may be undergoing racemizing equilibrating retro-Michael-Michael addition. However, based on the earlier NMR experiments, hypothesis A seems to be unlikely as 4-methoxybenzylidene Meldrum's acid **5b** disappeared over a period of time. Instead, 4-methoxybenzylidene acetone **6b** formed over a period of time via the racemizing equilibrating retro-Michael-Michael addition starting from enantiopure **4b**. Further, in order to validate the possible reversible retro-Michael/Michael addition reaction (Hypothesis B), we carried out a cross-over experiment of enantiopure product **4b** and benzylidene acetone **6a** in the presence of 10 mol% of catalyst **Q2** in chloroform (18 h, Scheme 4 A, see ESI). The formation of 4-methoxybenzylidene acetone **6b** and product **4a** unambiguously supported the hypothesis B for the reversible retro-Michael/Michael addition pathway. This clearly gives an insight that compound **4b** undergoes an elimination process to afford Meldrum's acid **1** and 4-methoxybenzylidene acetone **6b** over a period of time. Interestingly, longer reaction time also resulted in spiro compound **6b'** (4+2 cycloaddition of **5b** and **6b**, 35% yield)[6] along with racemic **4b** (see Scheme 4 B) and this finding further supported the hypothesis B.[9] This unexpected finding led us to believe that possibly the higher concentration of the catalyst **Q2** may be the key factor (acting as a base) for the retro-Michael/Michael addition thus causing erosion of enantiopurity. In order to overcome this problem, we planned to add acidic additive such as trifluoroacetic acid (20 mol% TFA, pKa 0.23) along with the catalyst to reduce the undesirable base effect of the catalyst. However, interestingly we observed that the initial excellent enantioselectivity eroded over the time (see red line,

Fig 2). Nevertheless, erosion of enantioselectivity was found to be relatively slower than in the presence of sole catalyst **Q2** (see black line, Fig 2).



Scheme 4. Crossover experiment to validate hypothesis B

This led us to believe that reducing the catalyst loading instead of compromising the reaction time would be more beneficial. It was gratifying to note that the reaction of **1**, **2b** and **3a** in presence of 1 mol% of **Q2** in chloroform (24 h) afforded the corresponding product **4b** in excellent enantioselectivity (93% *ee*), however, over a period of time very slow erosion of enantioselectivity was inevitable (see green line, Fig. 2). Gratifyingly, the addition of 2 mol% of TFA along with **Q2** (1 mol%) found to be highly effective and the enantiopurity of **4b** remained almost unchanged even after prolonged reaction time 72 h (see blue line, Fig. 2).

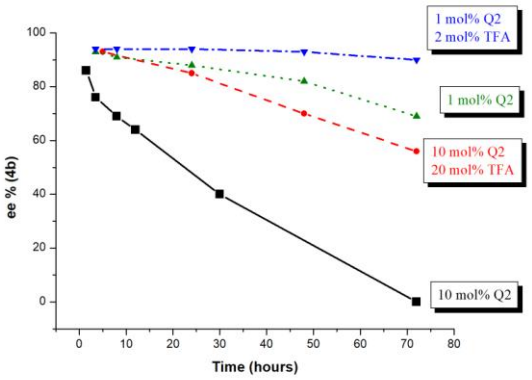
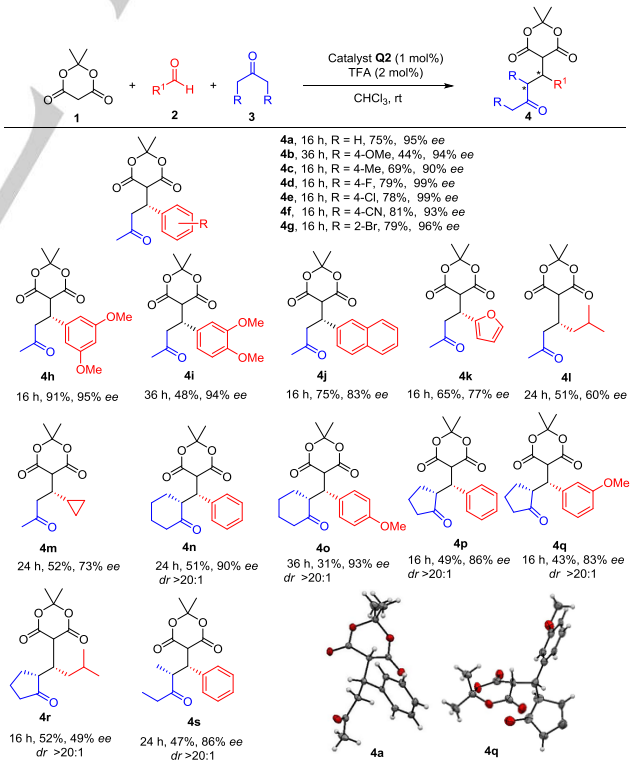


Figure 2. Effect of catalyst loading and time on enantioselectivity of **4b**

Based on our experimental observations and literature precedents[8c,8d] we propose that under higher catalyst loading the initially formed enantiopure product **4b**, slowly undergoes equilibrating retro Michael-Michael addition process thus leading to racemization (Step 2, Scheme 2). The more favourable increase in entropy could be the driving force for the irreversible racemization and would reach the completion when thermodynamic equilibrium is achieved (*ee* ≈ 0 %).[10] This assumption was further revalidated by the reaction of Meldrum's acid **1** and 4-methoxy benzylidene acetone **6b** in presence of 10 mol% of **Q2** and 20 mol% TFA (see Scheme 4C). [11] It is interesting to note that initially formed enatiomerically pure product (+)-**4b** (94% *ee*) was susceptible to the erosion of enantiopurity over a period of time (30 h, 72% ee). Further, treatment of isolated enantiopure product (+)-**4b** with 10 mol% of **Q2** over a period of time (72 h) resulted in almost racemic (±)-**4b**. On the other hand, under the lower catalytic loading (1 mol% **Q2** and 2 mol% TFA) due to the slower reaction rate Michael addition favours over racemizing retro-Michael/Michael pathway (Step 2, Scheme 2) resulting in the enantiomerically pure product (+)-**4b**. Further, the reaction of 4-methoxybenzylidene Meldrum's acid **5b** with acetone **3a** in the presence of 10 mol% of **Q2** and 20 mol% TFA afforded the enantiopure desired product (+)-**4b** in 2 h. However, prolonging this reaction (40 h) resulted in erosion in enantioselectivity leading to **4b** (72% ee) along with small amount of Meldrum's acid **1** and 4-methoxy benzylidene acetone **6b** (see Scheme 4D). Based on the above experiments and especially from scheme 4C & 4D, we can propose that enantiopure (+)-**4b** slowly undergoes retro-Michael-Michael reaction equilibrium to give racemic **4b** over the period of time.

Table 1. Substrate scope[(a-d)]



[a]Optimized Reaction Conditions: Meldrum's acid **1** (1 equiv.), aldehyde **2** (1.05 equiv.), ketone **3** (5 equiv.) catalyst **Q2** (1 mol%), TFA as an additive (2 mol%), in chloroform at rt; [b]isolated yield after purification by column chromatography given in parenthesis; [c]*dr* was calculated based ^{1}H NMR; [d]*ee* was determined by HPLC using chiral column.

Based on the available experimental evidences we can surmise the most probable mechanistic pathway for the erosion in the enantioselectivity. After re-establishing the optimum catalytic loading (1 mol% **Q2** and 2 mol% TFA) we explored the generality of the reaction by using various aldehydes and ketones. The aromatic aldehydes, both electron-rich and -deficient were found to be compatible under the optimized reaction conditions by affording the corresponding products (**4a-4j**, Table 1) in good yields with excellent enantioselectivity up to 99% *ee.* However, we observed that aromatic aldehydes such as 4-methoxy benzaldehyde and 3,4-dimethoxy benzaldehyde reacted relatively slow (36 h) affording **4b** and **4i**.[9] Heteroaromatic aldehyde such as furfural, worked well under the reaction conditions and afforded the corresponding **4k** in good yield with relatively lower enantioselectivity (77% *ee*). In order to have a wider scope, further, we examined the feasibility of reaction on the aliphatic aldehydes. It was found that even the enolizable aldehydes were well tolerated in the presence of primary amine catalyst **Q2**, affording the products (**4l** and **4m**) in good yields with moderate enantioselectivity (60-73% *ee*). The scope of the reaction was extended further towards substituted Michael donors such as cyclohexanone, cyclopentanone and 3-pentanone with various aldehydes. In all the cases corresponding products (**4n-4s**) were obtained as single diastereomers with moderate to excellent enantioselectivity (up to 94% *ee*). Notably, this protocol tolerated a wide variety of aldehydes under very mild reaction conditions. The strength and practicality of this protocol was also demonstrated on a gram scale synthesis of product **4a** (74% yield) without loss of enantioselectivity (94% *ee*) under optimized reaction conditions.
In order to show the wider applicability of this protocol we demonstrated enantiopure synthesis of some of the important precursors of many useful molecules such as carboxylic acid, ester and amide starting from **4a** (see ESI, page S25). The synthesis of ester also helped to identify the absolute configuration of **4a** (see ESI).[12] Based on these findings the absolute configuration of **4a** was assigned as '*R*'.

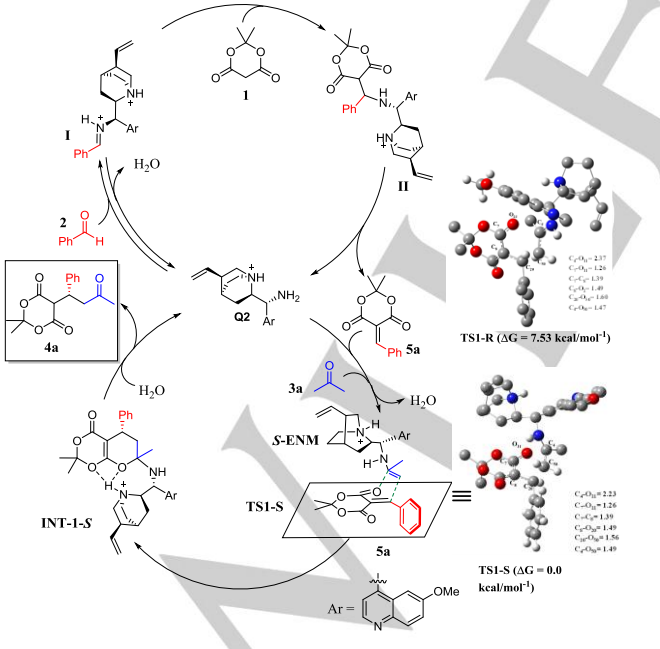


Figure 3. Proposed mechanism[a,b]
[a]Transition state structures for the addition of enamine *S*-ENM to **5a** (both *si* and *re* face); [b]selected bond distances are in Å; relative free energies are given in parenthesis (kcal·mol^{-1}); M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d). Most of the H-atoms have been omitted for the sake of clarity.

The molecular structure of compounds **4a** and **4q** (relative configuration) were established using single crystal X-ray diffraction analysis (Table 1). [13]
The proposed mechanism was computationally studied using the density functional theoretical calculations (see ESI for results and details). Initially protonated primary amine **Q2** catalyzes Knoevenagel condensation via iminium ion intermediate (I) and intermediate (II) to generate a heterodiene (**5a**). In the second step catalyst **Q2** forms chiral enamine (*S*-ENM) with acetone **3a** that further reacts with the heterodiene (**5a**) via [4+2]-hetero-Diels-Alder cycloaddition pathway.[14] The transition states (TS's) for the [4+2] cycloaddition step could follow the enamine/**5a** *si* facial attack or enamine/**5a** *re* facial attack, thus resulting in TS1-*S* and TS1-*R* TS's, respectively (Fig. 3). Of these two TS's formed, TS1-*S* is 7.53 kcal/mol more stable than the TS1-*R* resulting in product **4a** (*R* configuration) with high stereoselectivity (Theoretical *ee* = 98% is in very good agreement with the experimental *ee* = 95% see ESI).

In conclusion, we demonstrated highly enantioselective organocatalytic multicomponent reaction of aldehyde, ketone and Meldrum's acid for the first time since its discovery. We carried out a systematic study on the adverse effect of higher catalytic loading and longer reaction time on the outcome of enantioselectivity. In order to understand the mechanism of racemization in depth further detailed investigation is needed. The protocol worked efficiently under very low catalyst loading (1 mol%) and proved to be scalable. The protocol is practical as it gives a quick access to very useful precursors and intermediates such as enantiopure *δ*-keto esters, carboxylic acids and amides. This mild and useful reaction may find a wider application in future**.**

Acknowledgements

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Keywords: Multicomponent reaction • Organocatalysis • Adverse effect • Enantioselectivity • Hetero-Diels-Alder cycloaddition

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afforded corresponding compounds **4b, 4i** along with modest amount (30-35%) of corresponding spiro compounds.

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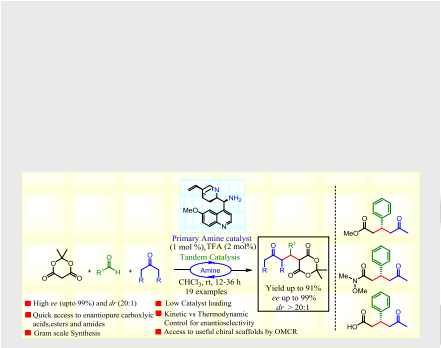

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