Sequential one-pot combination of multi-component and multi-catalysis cascade reactions: an emerging technology in organic synthesis†

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Creating sequential one-pot combinations of multi-component reactions (MCRs) and multi-catalysis cascade (MCC) reactions is a challenging task that has already emerged as a new technology in synthetic organic chemistry. Through one-pot sequential combination of MCRs/MCC reactions, the chemical products (fine chemicals, agrochemicals and pharmaceuticals) that add value to our lives can be produced with less waste and greater economic benefits. Within this Emerging Area, we describe our recent developments and designs for sequential one-pot MCRs/MCC reactions to facilitate their realization as biomimetics in organic chemistry.

Introduction

The very intense efforts the organic chemistry community has made must be appreciated for the reason that most complex functionalized molecules can be synthesized, but lengthy processing times, wasteful and expensive routes are often required. Thus, targets of most practical use, for example fine chemicals, agrochemicals, pharmaceutical drugs, drug intermediates and ingredients, can be challenging to produce even if they are only moderately complex. We strongly believe that organic synthesis can be made much more efficient by designing processes in which multiple catalysts operate sequentially in "one-pot" with multiple components. Ultimately, this one-pot sequential combination of multi-catalysis and multi-component approach should reduce the cost and waste associated with pharmaceutical synthesis (see Scheme 1).

The increasing demands for environmentally and economically friendly synthetic processes promote the development of one-pot sequential combination of multi-catalysis and multi-component systems to provide the desired products in the most efficient ways.[1] Understanding and practice of this concept may be taken from cellular reactions, in which numerous enzymes catalyze

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† Dedicated with respect to Professor Carlos F. Barbas III, for his outstanding contributions to the area of organocatalysis.

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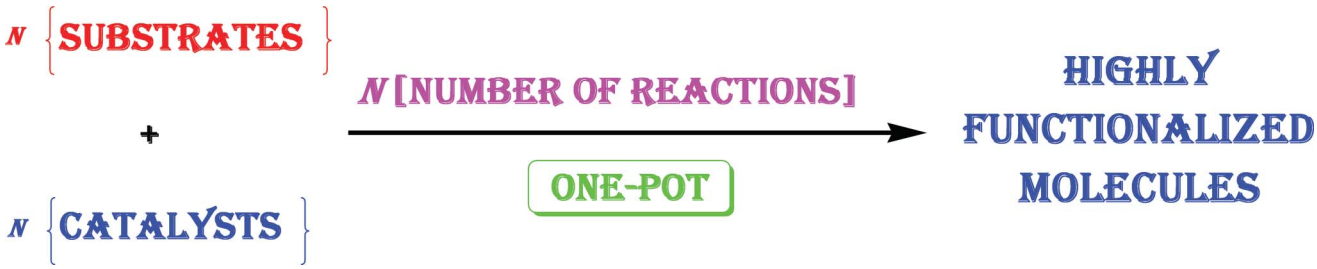


Scheme 1 Combining multi-catalysis and multi-component systems for the one-pot synthesis of complex molecules.

multi-reactions in one-pot with a sequential manner from multi-components.[2]

Interestingly, an instructive example has been demonstrated by A. Ian Scott and co-workers in 1994, that of *in vitro* synthesis of corrin from 5-aminolevulinic acid using 12 enzymes with an overall yield of 20% in a total of 17 steps in a single flask.[3] Mimicking this type of bio-catalysis by artificial chemical catalysis would be a great interest for chemists. In this regard, extensive studies have been conducted on the preparation and utilization of multi-functionalized catalyst systems in organic synthesis. For example, catalysts that contain both Lewis acidic and basic sites have been elegantly utilized for the simultaneous activation of substrates and reagents, making possible multiple cascade reactions in one-pot.[4] Despite the significant developments recently achieved, increasing the number of starting components, and accurately predicting the binding mode and the interaction between substrates and catalysts is still in the early stages, and thus the more systematic design and synthesis of multi-functional catalysts is still developing.

Recent developments in amine- or amino acid-catalyzed cascade and multi-component reactions[5] give promise that this kind of mild catalysis is suitable for the design of sequential combination of multi-catalysis and multi-component reactions in one-pot to deliver highly functionalized molecules compared to classical reactive metal-mediated reactions.

In 2004, Ramachary and Barbas first disclosed multiple reactions taking place in one-pot under multiple catalytic conditions to generate functionalized molecules through organocatalysis as basic platform.[6] This discovery stimulated interest in the design of related transformations and a significant number of cascades involving combination of multiple components and multiple amine-based organocatalysts have been developed by potential variation of the reaction conditions over the last few years.[7] These conditions have allowed the combination of multiple reactive functionalities such as active olefins, aldehydes, ketones, imines, nitroalkanes, CH-acids and other pro-nucleophiles by providing three crucial activation methods: iminium activation of α,β-unsaturated carbonyl compounds, enamine activation of carbonyl compounds and self-activation of olefins by providing suitable electron withdrawing groups. These three activation methods in combination have facilitated some incredibly elegant transformations of relatively simple starting materials to complex molecular architectures like cellular-type biochemical reactions.

In this Emerging Area, we describe the first systematic efforts toward the development of sequential one-pot combinations of multi-component reactions (MCRs) and multi-catalysis cascade (MCC) reactions through three-component reductive alkylation (TCRA) and push-pull dienamine (PPD) reactions as basic platforms that add a new dimension to catalytic reactions. The initiation reaction of the sequential one-pot combination of MCRs/MCC reactions must be modular, multi-functional, high-yielding and orthogonal in nature like a click reaction.[8] In this context, we have developed new TCRA and PPD reactions as novel arsenal to achieve all above mentioned reaction motifs and also joined the club of click reactions.

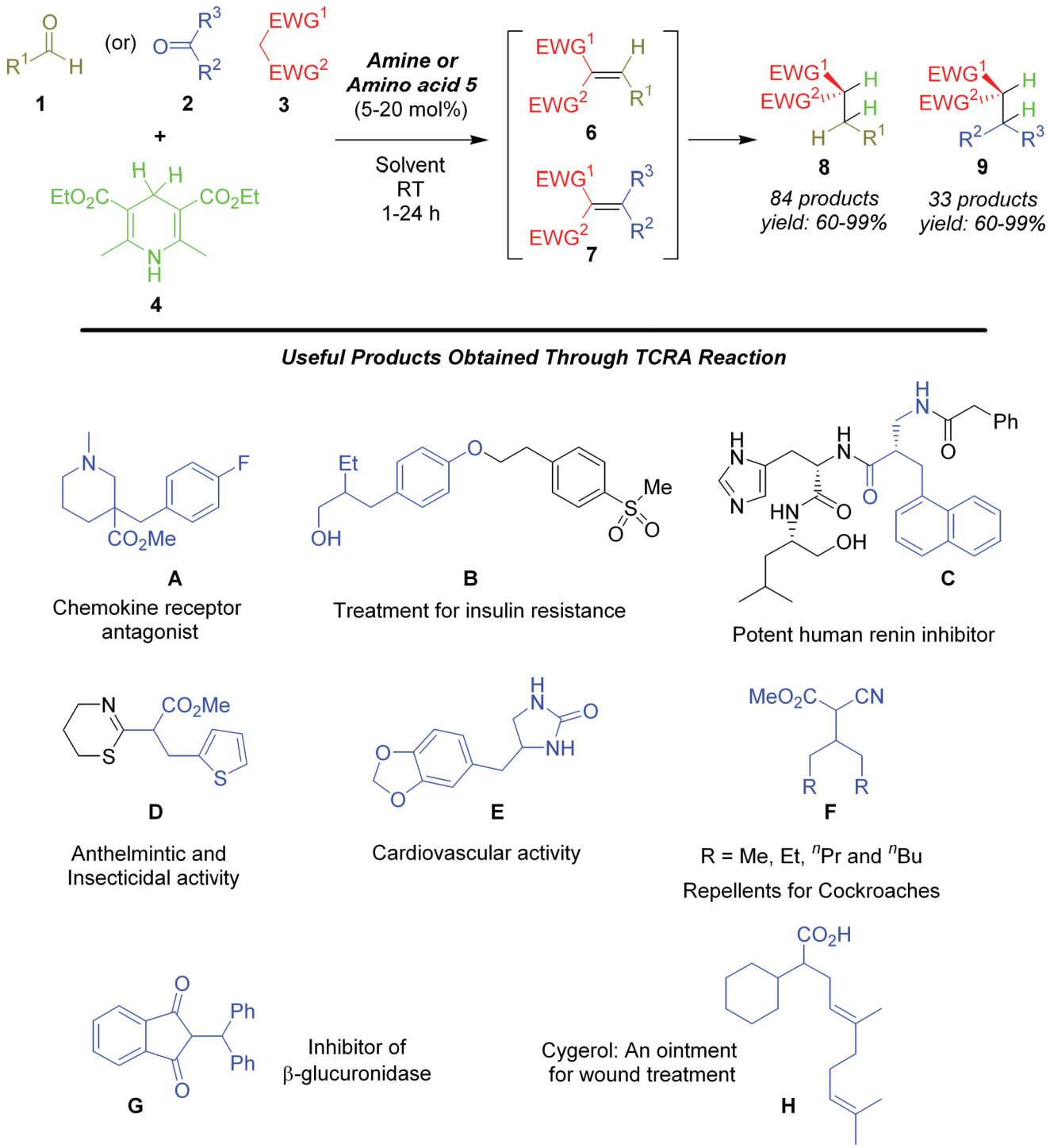
Development of TCRA reactions in one-pot

In 2006, first we focused on the optimization of high-yielding syntheses of a variety of TCRA products **8/9** from **1**, **2**, **3** and **4** through amine- or amino acid-catalysis, which is preliminary reaction for designed sequential one-pot combination of MCRs/MCC reactions (Scheme 2).[9a–c] For that we did our studies on the development of cascade TCRA reaction by screening a number of known and novel organocatalysts **5** for the reductive alkylation of a variety of CH-acids **3** with variety of aldehydes **1** or ketones **2** and Hantzsch ester **4** as shown in Scheme 2.[9] Under the proline-catalyzed TCRA process, first highly reactive and substituted olefin species **6** and **7** are generated *in situ* under very mild and environmentally friendly conditions *via* iminium activation, thus giving the hydrogenated products **8** and **9** through the action of Hantzsch ester **4** by self-catalysis through decreasing the HOMO–LUMO energy gaps between olefins **6/7** and Hantzsch ester **4** through biomimetic reductions.[10] Highly functionalized diverse TCRA compounds **8/9** are biologically active products and have wide pharmaceutical applications (see **A–H**), which were assembled from simple substrates such as aldehydes **1**, ketones **2**, CH-acids **3**, and Hantzsch ester **4** by diversity-oriented green synthesis in one-pot.[9a–c] The generality of the cascade TCRA reaction was demonstrated by producing 84 products **8** with 60–99% yields and 33 products **9** with 60–99% yields as shown in Scheme 2.[9a–c]

Development of TCRA reactions with multi-functional aldehydes/ketones in one-pot

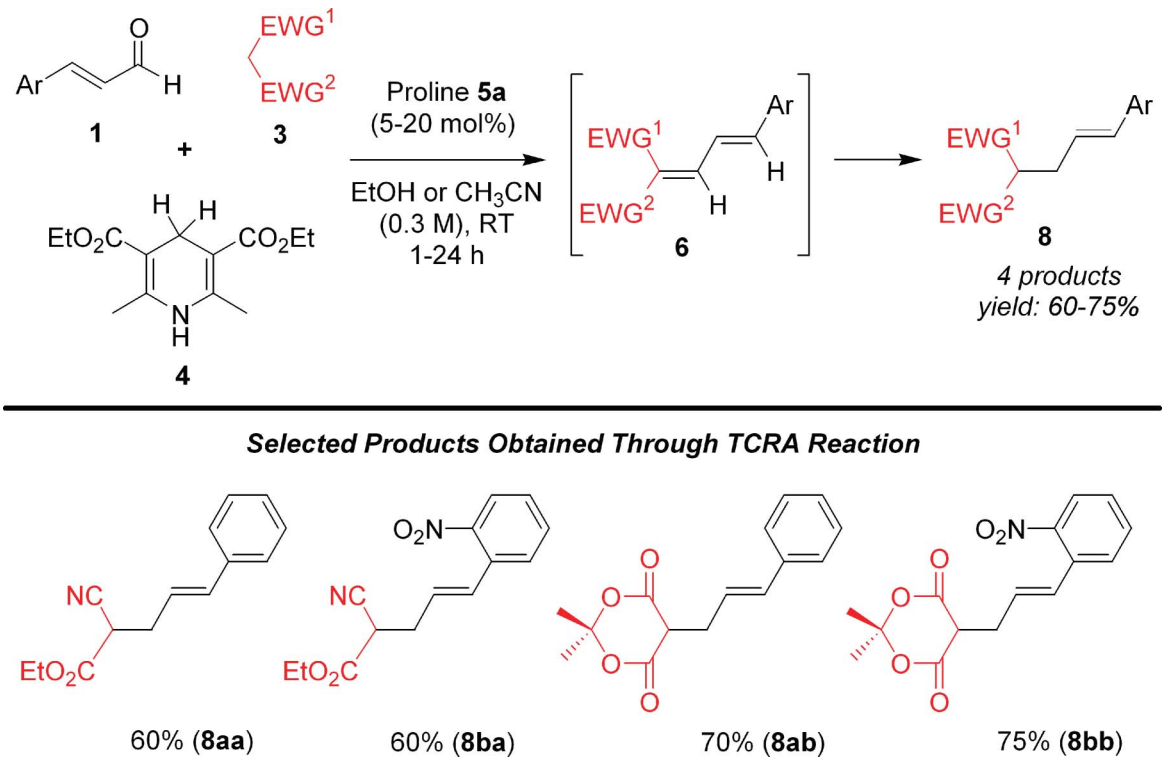
Interestingly cascade TCRA reaction of (*E*)-cinnamaldehyde **1a** or (*E*)-2-nitrocinnamaldehyde **1b** with CH-acids **3a–b** and Hantzsch ester **4** under proline-catalysis furnished the hydrogenated products **8aa–8bb** in good yields with high regioselectivity as shown in Scheme 3 and this kind of selectivity may not be possible under the classical reduction conditions.[9]

In continuation of understanding the proximity effect in TCRA reactions, proline-catalyzed cascade TCRA reaction of Meldrum's acid **3b** with 2-hydroxy-benzaldehyde **1c** and Hantzsch ester **4** at 25 °C in MeOH furnished the unexpected



Scheme 2 Development of TCRA reactions in one-pot and their synthetic applications.

cascade TCRA/hydrolysis (TCRA/H) product mono-methyl 2-(2-hydroxy-benzyl)malonate **8cd** with very good yield (Scheme 4).[9] Interestingly, water-promoted cascade TCRA reaction of Meldrum's acid **3b** with 2-hydroxy-benzaldehyde **1c** and Hantzsch ester **4** at 25 °C in water furnished unexpected cascade TCRA/H product 2-oxo-chroman-3-carboxylic acid **10cb** with good yield (Scheme 4). Also, water-promoted cascade TCRA reaction of malononitrile **3c** with 2-hydroxy-benzaldehyde **1c** and Hantzsch ester **4** at 70 °C in water furnished unexpected cascade TCRA/H product 2-amino-4*H*-chromene-3-carbonitrile **10cc** with very good yield (Scheme 4). Formation of unexpected cascade TCRA/H products **8cd**, **8ce**, **10cb** and **10cc** from **1c**, **3b**, **3c** and **4** under with and without proline-catalysis in MeOH, EtOH and H_2O respectively can be explained as shown in Scheme 4. Inter- and intra-molecular hydrolysis of *in situ* generated cascade TCRA products **8cb** and **8cc** with solvents like MeOH/EtOH or H_2O



Scheme 3 Observation of high regioselectivity in TCRA reactions.

gives the cascade TCRA/H products **8cd**, **8ce**, **10cb** and **10cc** respectively. These two different types of hydrolysis are possible due to the nucleophilic nature of alcoholic solvents and possibility of more weak interactions in water.

Sequential combination of TCRA with alkylation in one-pot

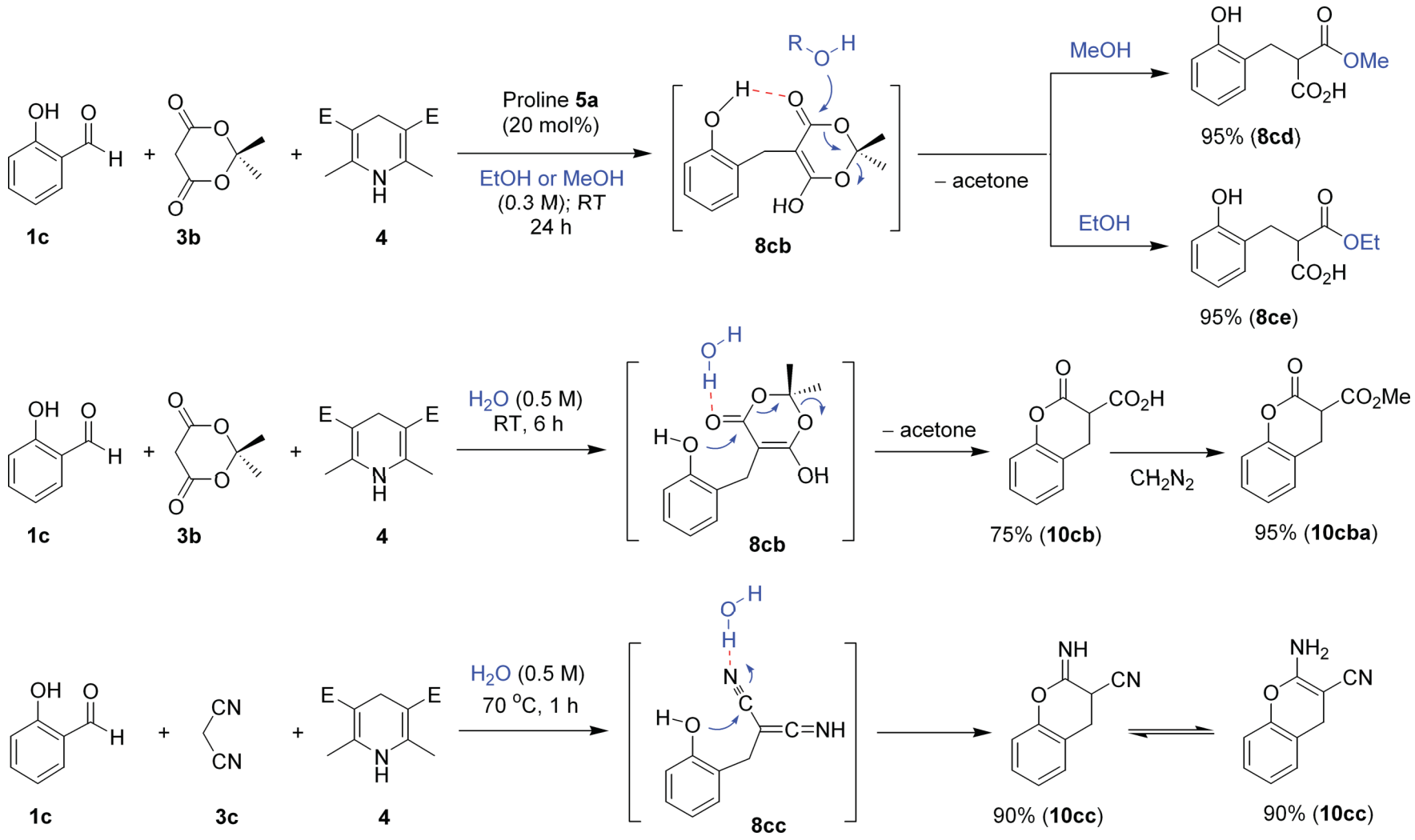
After successful understanding of the proline-catalyzed TCRA reactions with various aldehydes **1** or ketones **2** and CH-acids **3**, we engineered a novel proline/K_2CO_3-catalyzed four-component TCRA/alkylation (TCRA/A) reaction of aldehydes **1** or ketones **2**, ethyl cyanoacetate **3a** or malononitrile **3c**, Hantzsch ester **4** and alkyl halides **11** in one-pot (Scheme 5).[9] Highly substituted cyano-esters **12/13** containing a quaternary carbon were constructed in good yields with various substitutions as shown in Scheme 5 and this process is the first example of the utility of the proline/K_2CO_3 combination in green catalysis.[9] One-pot TCRA/A products **12/13** have direct applications in pharmaceutical and agricultural chemistry, for example ethyl (4-chlorobenzyl)cyano-methyl-acetate **K** is anti-inflammatory active,[9c] ethyl 2-(2-chlorobenzyl)-2-cyanobutyrate **L** is analgesically active,[9c] 2-allyl-2-(4-chlorobenzyl)malononitrile **J** is a very good pesticide,[9c] which showed 100% control against *Musca domestica* and German cockroach and these results emphasize the value of this sequential combination of TCRA with alkylation approach.

Sequential combination of TCRA with hydrogenation in one-pot

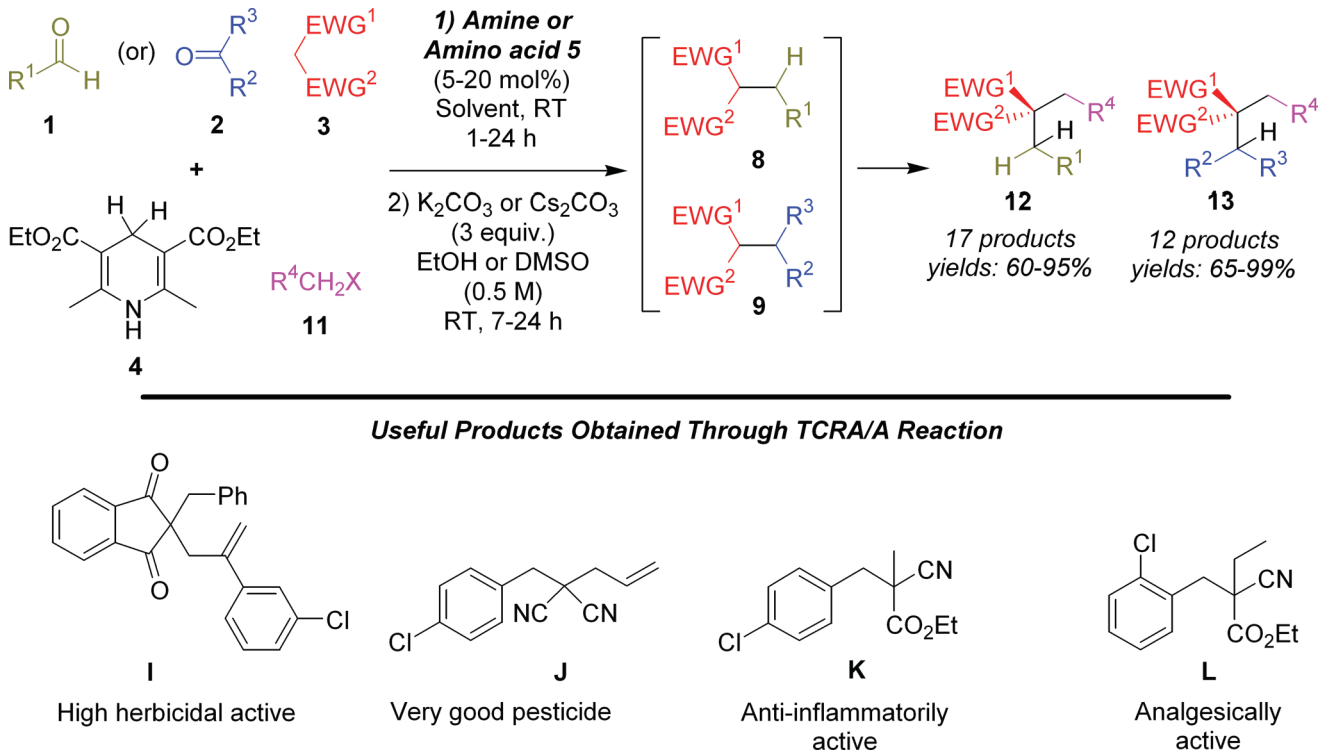
Recently List *et al.* demonstrated the morpholine/CF_3CO_2H-catalyzed hydrogenation of α,β-unsaturated aldehydes **1a** and **1b** with Hantzsch ester **4** to furnish the saturated aldehydes **1d** and **1e**, respectively with good yields.[11] For the development of sequential cascade double hydrogenation reactions in one-pot, we have utilized the List's hydrogenation-technique to obtain the saturated aldehydes **1d** and **1e** *in situ* from α,β-unsaturated aldehydes **1a** and **1b** and further reacted with CH-acid **3b** and Hantzsch ester **4** to generate the highly functionalized CH-acids **8** with good yields in one-pot as shown in Scheme 6.[9c] Sequential combination of amine/acid- and self-catalyzed cascade double hydrogenation reactions will surely show much impact on synthetic sequences, which can be utilized in the total synthesis of natural products.

Observation of *SSC* as dominating factor rather than *PSC* in TCRA reactions

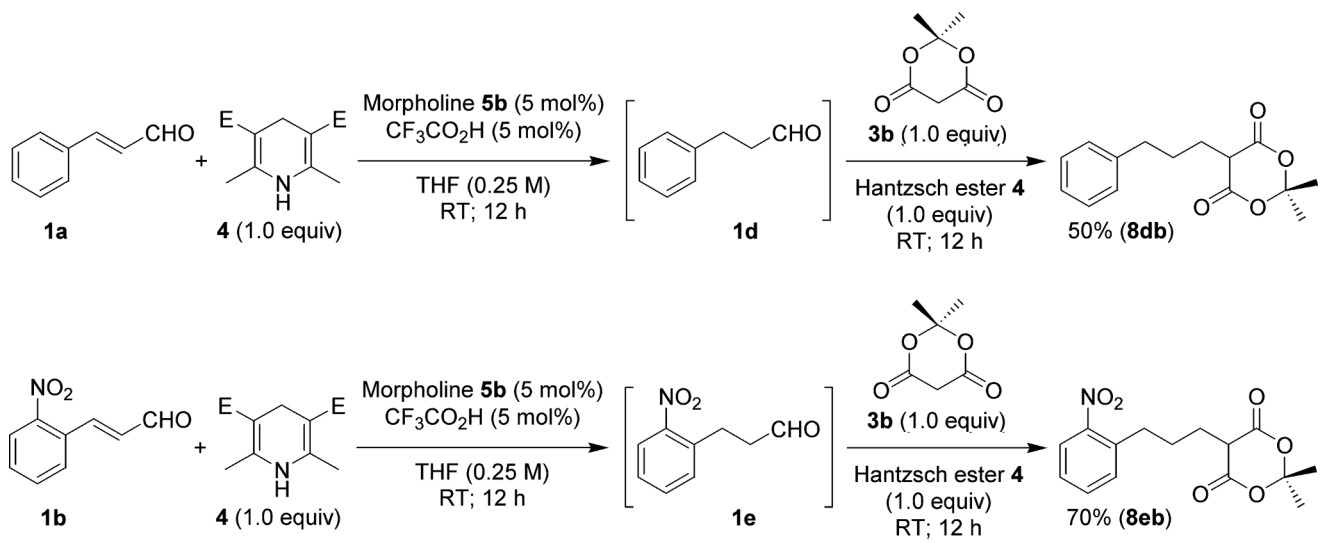
With an ideal cascade TCRA protocol in hand, the scope of the TCRA reactions was investigated with various functionalized ketones **2** and CH-acids **3** by generating highly useful diversity-oriented library of **9**.[9b,c] Cascade TCRA reaction of 4-ᵗbutylcyclohexanone **2a**, ethyl cyanoacetate **3a** and Hantzsch ester **4** furnished the regioselective ester *cis*-**9aa** in 6 : 1 ratio with 95% yield. Cascade TCRA reaction of cyclohexane-1,4-dione **2b** with CH-acids **3a**/**3a′** and Hantzsch ester **4** under proline-catalysis furnished the double cascade products **9ba** and **9ba′** in good yields with high selectivity as shown in Scheme 7. Cascade TCRA reaction of highly substituted cyclohexanones **2c**/**2d** with CH-acids **3a**/**3c** and Hantzsch ester **4** under proline-catalysis furnished the cascade products **9ca**, **9da** and **9dc** in good yields with high selectivity as shown in Scheme 7.[9b,c]



Scheme 4 Observation of proximity effect in TCRA reactions.



Scheme 5 Sequential combination of TCRA with alkylation in one-pot.

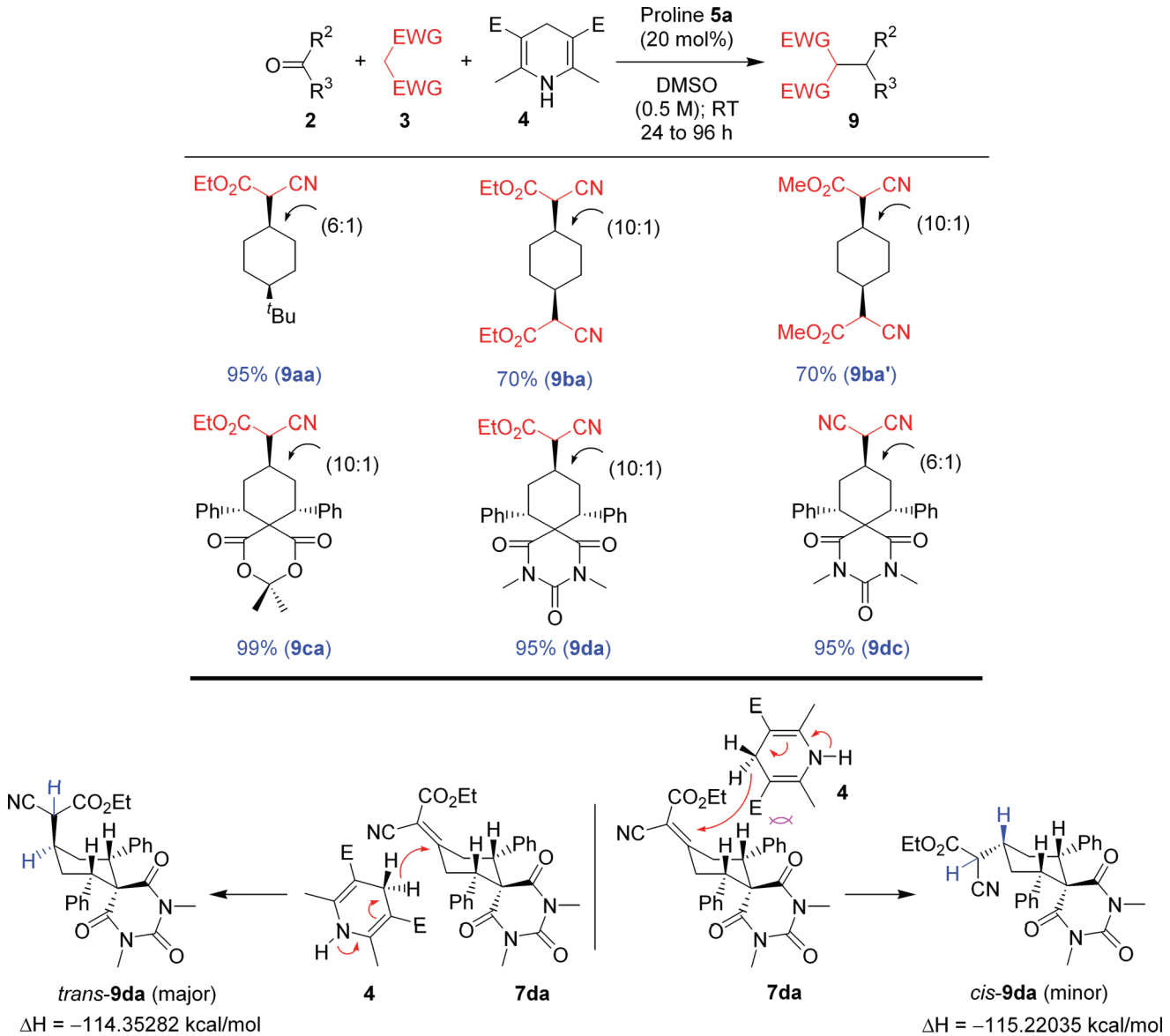


Scheme 6 Sequential combination of TCRA with hydrogenation in one-pot.

The observed high regioselectivity in cascade products **9** can be explained as shown in Scheme 7. Here approach of the hydride source (Hantzsch ester **4**) to olefin **7** is the main controlling factor rather than the thermodynamic stability of the resulting hydrogenated products **9**. Approach of the Hantzsch ester **4** to olefin **7da** through an equatorial position is more favoured than through an axial position, which may be due to the existence of more steric hindrance in an axial approach. As shown in Scheme 7, steric strain control (SSC) is the main controlling factor rather than product stability control (PSC) in bio-mimetic cascade reductions, because thermodynamically stable isomer *cis*-**9da** is formed as minor product. This selectivity trend can be easily understood by the approach of bulk hydride source **4** to olefins **7**.[9b,c]

Development of TCRA as click reactions

After successful demonstration of Hantzsch ester **4** as an organic-hydride in TCRA reactions, we further showed interest in improving the reaction efficiency by producing both olefin and organic-hydride *in situ* to call it a click reaction. For this we developed the economic and



Scheme 7 Observation of *SSC* as dominating factor rather than *PSC* in TCRA reactions.

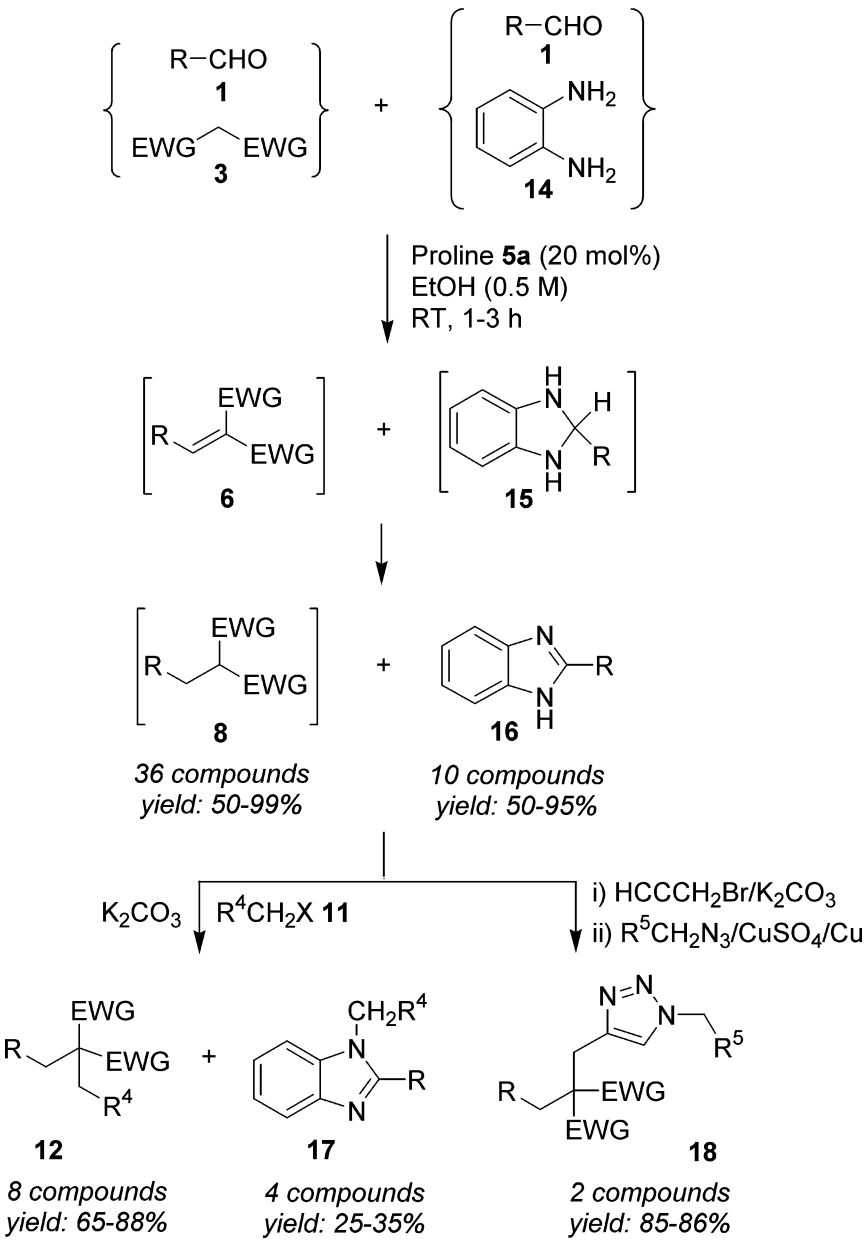
environmentally friendly biomimetic one-pot three and four-component olefination/hydrogenation (O/H), five-component olefination/hydrogenation/alkylation (O/H/A) and six-component olefination/hydrogenation/alkylation/Huisgen cycloaddition (O/H/A/HC) reactions of aldehydes **1**, CH-acids **3**, *o*-phenylenediamine **14**, alkyl halides **11** and azides using proline **5a**, proline/metal carbonate and proline/metal carbonate/Cu^{I}-catalysis (Scheme 8).[12] Many of the main products O/H **8**, O/H/A **12** and O/H/A/HC **18** compounds and by-products **16** and **17** are furnished in good yields and show direct applications in pharmaceutical chemistry.

These reactions have many advantages over classical reductions: simple mixing of reactants in an open vial, *in situ* generation of both olefin and hydride, >99% chemoselectivity and no aqueous work-up, simple filtration for purification and very good yields.[12]

Taking inspiration from nature's approach, we addressed the development of a set of powerful, highly reliable, and selective cascade reactions for the rapid synthesis of useful pharmaceutical intermediates and ingredients through proline-/metal carbonate- and Cu^{I}-catalyzed olefination, hydrogenation, alkylation and Huisgen cycloaddition reactions, an approach we called "organo-click reactions" (Scheme 8).[12] Recently, Sharpless and co-workers introduced the concept of click chemistry.[8] Later on Ramachary and Barbas combined organocatalytic reactions with click chemistry (organo-click chemistry).[6] Ideally, organocatalytic TCRA reactions also fulfil all the aspects of click reaction conditions, such as the reactions must be modular, wide in scope, high yielding, generate only inoffensive by-products, and be stereospecific.

Sequential combination of TCRA with Robinson annulation, aromatization and *O*-alkylation in one-pot

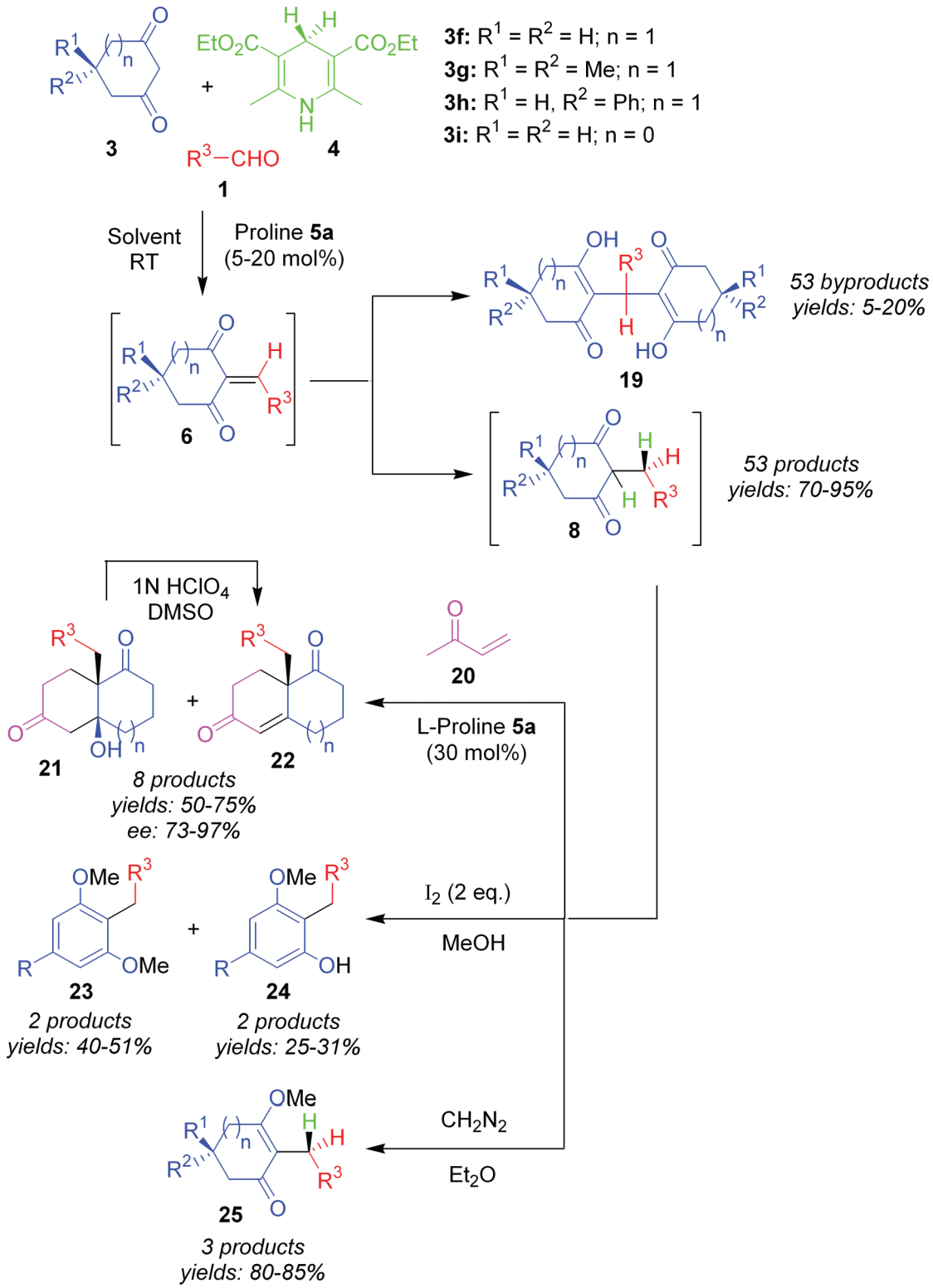
In 2007, with synthetic and pharmaceutical applications in mind, we further extended the sequential combination of TCRA



Scheme 8 Towards organo-click reductions in one-pot.

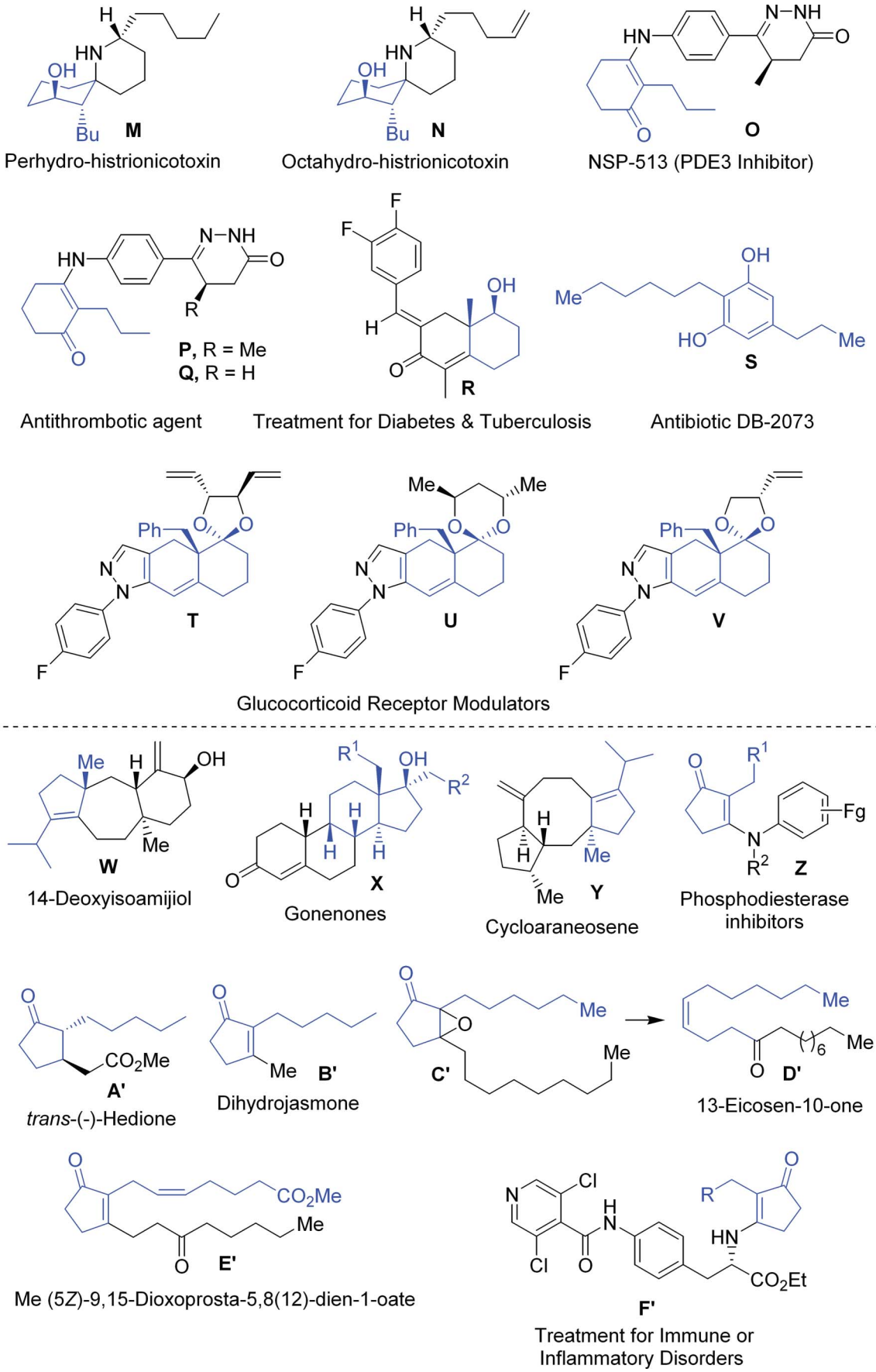
with Robinson annulation, aromatization and *O*-alkylation reactions in one-pot to furnish the important drug intermediates as shown in Schemes 9 and 10.[13] A practical and novel organocatalytic chemo- and enantioselective process for the cascade synthesis of highly substituted 2-alkylcyclohexane-1,3-diones **8**, 2-alkylcyclopentane-1,3-diones **8**, Wieland–Miescher (W–M) ketone analogs **22** and Hajos–Parrish (H–P) ketone analogs **22** was presented *via* TCRA as a key step. In this work, we developed the one-step alkylation of dimedone **3g**, 1,3-cyclohexanedione **3f** and 1,3-cyclopentanedione **3i** with aldehydes **1** and Hantzsch ester **4** through organocatalytic reductive alkylation strategy.[13] Direct combination of L-proline-catalyzed cascade TCRA and cascade Robinson annulation (RA) of CH-acids (1,3-cyclohexanedione **3f** and 1,3-cyclopentanedione **3i**), aldehydes **1**, Hantzsch ester **4** and methyl vinyl ketone **20** furnished the highly functionalized W–M ketone and H–P ketone analogs **22** in good to high yields and with excellent enantioselectivities (Scheme 9). Many of these TCRA and TCRA/RA products showed direct application in pharmaceutical chemistry as shown in Scheme 10.[13a,b]

2-Alkylcyclohexane-1,3-diones **8** are readily transformed into substituted mono-methyl and dimethyl resorcinols **23**/**24** with iodine and methanol as shown in Scheme 9.[13a] The substituted resorcinol unit is a basic building block for a large number of valuable naturally occurring polyketide metabolites.[13a] Highly substituted resorcinols have gained importance in recent years as starting materials and intermediates for the synthesis of cannabinoids and benzochroman derivatives, which possess a wide range of physiological and pharmacological properties.



Scheme 9 Sequential combination of TCRA with Robinson annulation, aromatization and *O*-alkylation in one-pot.

TCRA products 2-alkylcyclopentane-1,3-diones **8** are readily transformed into substituted 2-alkyl-3-methoxycyclopent-2-enones **25** by treatment with ethereal solution of diazomethane in one-pot as shown in Scheme 9.[13b] The highly functionalized 2-alkyl-3-methoxycyclopent-2-enone unit is a basic building block for a large number of valuable naturally occurring products.[13b] Highly functionalized 2-alkyl-3-methoxycyclopent-2-enones **25** have gained importance in recent years as starting materials and intermediates for the synthesis of prostaglandin analogues, which possess a



Scheme 10 Applications of TCRA and TCRA/RA products.

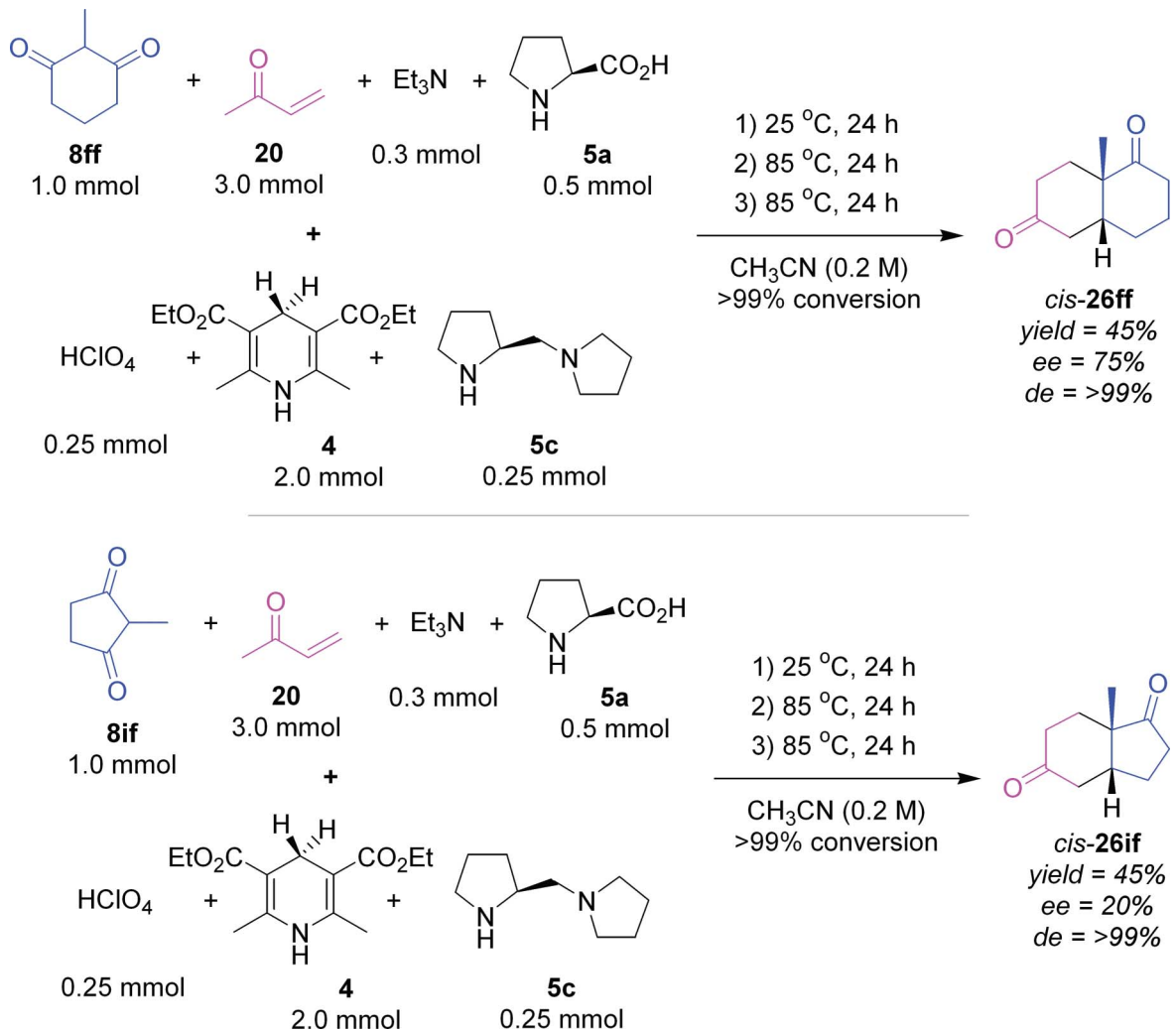
wide range of physiological and pharmacological properties (Scheme 10).

After successful one-pot demonstration of biomimetic asymmetric synthesis of W–M, H–P ketones and their analogs *via* TCRA and TCRA/RA reactions, we further investigated the one-pot asymmetric synthesis of hydrogenated W–M and H–P ketones *cis*-**26ff** and *cis*-**26if** *via* a combination of multi-catalysis and multi-component reactions in a single flask (Scheme 11).[14] Hydrogenated W–M ketone *cis*-**26ff** was furnished in 45% yield with 75% ee and >99% de through combination of three-components and four-catalysts in one-pot as shown in Scheme 11. Successful combination of multi-catalysis and multi-component reactions under amine-, amino acid-, acid- and amine/acid-catalysis was demonstrated by one more example as shown in Scheme 11 and this one-pot synthetic strategy should be showing much impact on asymmetric synthesis of functionalized small molecules.[14] Interestingly, this strategy did not show much difference in terms of enantioselectivity compare to two-component reaction under amino acid-catalysis for hydrogenated W–M ketone *cis*-**26ff** synthesis; but a difference was shown in one-pot synthesis of hydrogenated H–P ketone *cis*-**26if**.[14]

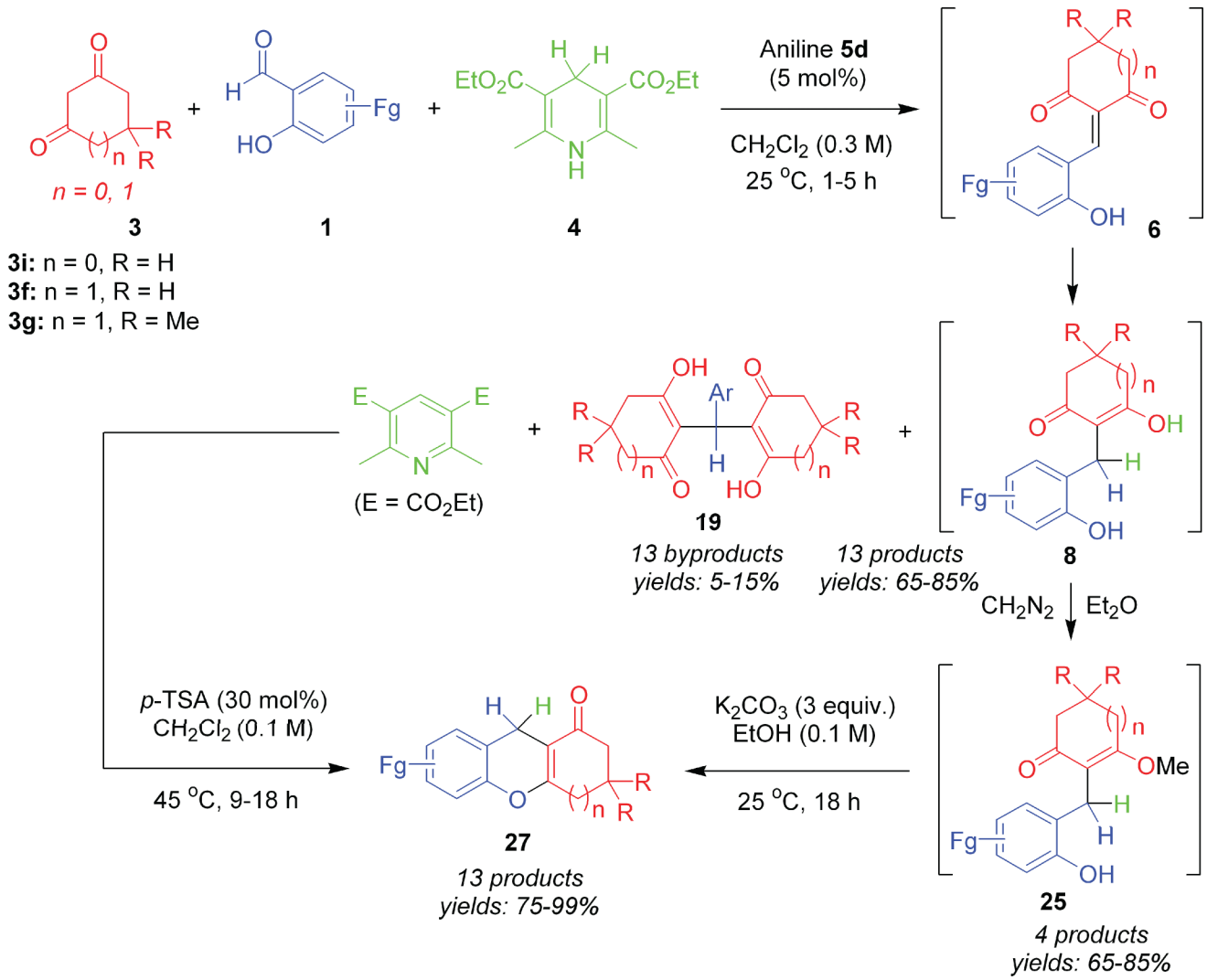
Sequential combination of TCRA with *O*-alkylation, oxy-Michael and dehydration reactions in one-pot

Heterocycles such as chromanes, chromenes, coumarins and tetrahydroxanthenones are of considerable importance in a variety of industries. These heterocycles are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry and polymer science.[15]

In 2008, we discovered a novel combination of MCR/MCC technology for the synthesis of highly substituted 2,3,4,9-tetrahydroxanthen-1-ones **27** and 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones **27** by using direct organocatalytic sequential one-pot TCRA/oxy-Michael/dehydration (TCRA/OM/DH) and TCRA/alkylation/oxy-Michael/dehydration (TCRA/A/OM/DH) reactions from commercially available functionalized 2-hydroxybenzaldehydes **1**, cyclopentane-1,3-dione **3i** or substituted cyclohexane-1,3-diones **3f**/**3g** and Hantzsch ester **4** (Scheme 12).[16] Direct combination of aniline-catalyzed cascade TCRA and *p*-TSA-catalyzed cascade



Scheme 11 Sequential combination of multi-catalysis and multi-component systems for the one-pot asymmetric reactions.



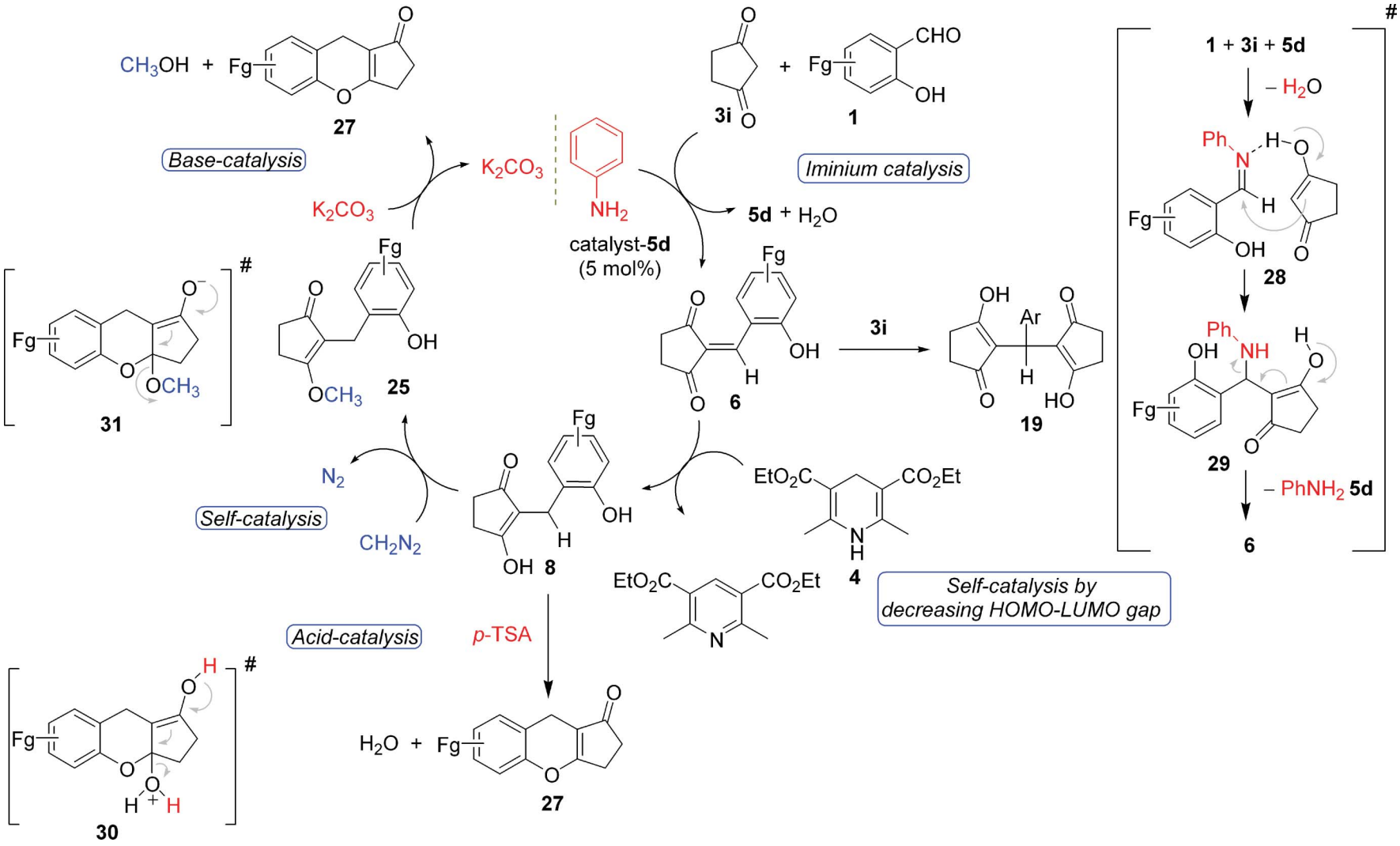
Scheme 12 Combining multi-catalysis and multi-component systems for the synthesis of heterocycles.

oxy-Michael/dehydration (OM/DH) or combination of aniline-catalyzed cascade TCRA and self-/K_2CO_3-catalyzed cascade alkylation/oxy-Michael/dehydration (A/OM/DH) of 1,3-diones **3**, salicylic aldehydes **1**, Hantzsch ester **4** and diazomethane was developed in one-pot for the synthesis of heterocycles as shown in Scheme 12.[16] A library of 2,3,4,9-tetrahydroxanthen-1-ones **27** and 3,9-dihydro-2*H*-cyclopenta[*b*]chromen-1-ones **27** was furnished in 75–99% yields, which provides useful starting materials for the synthesis of natural products and their analogues.[16]

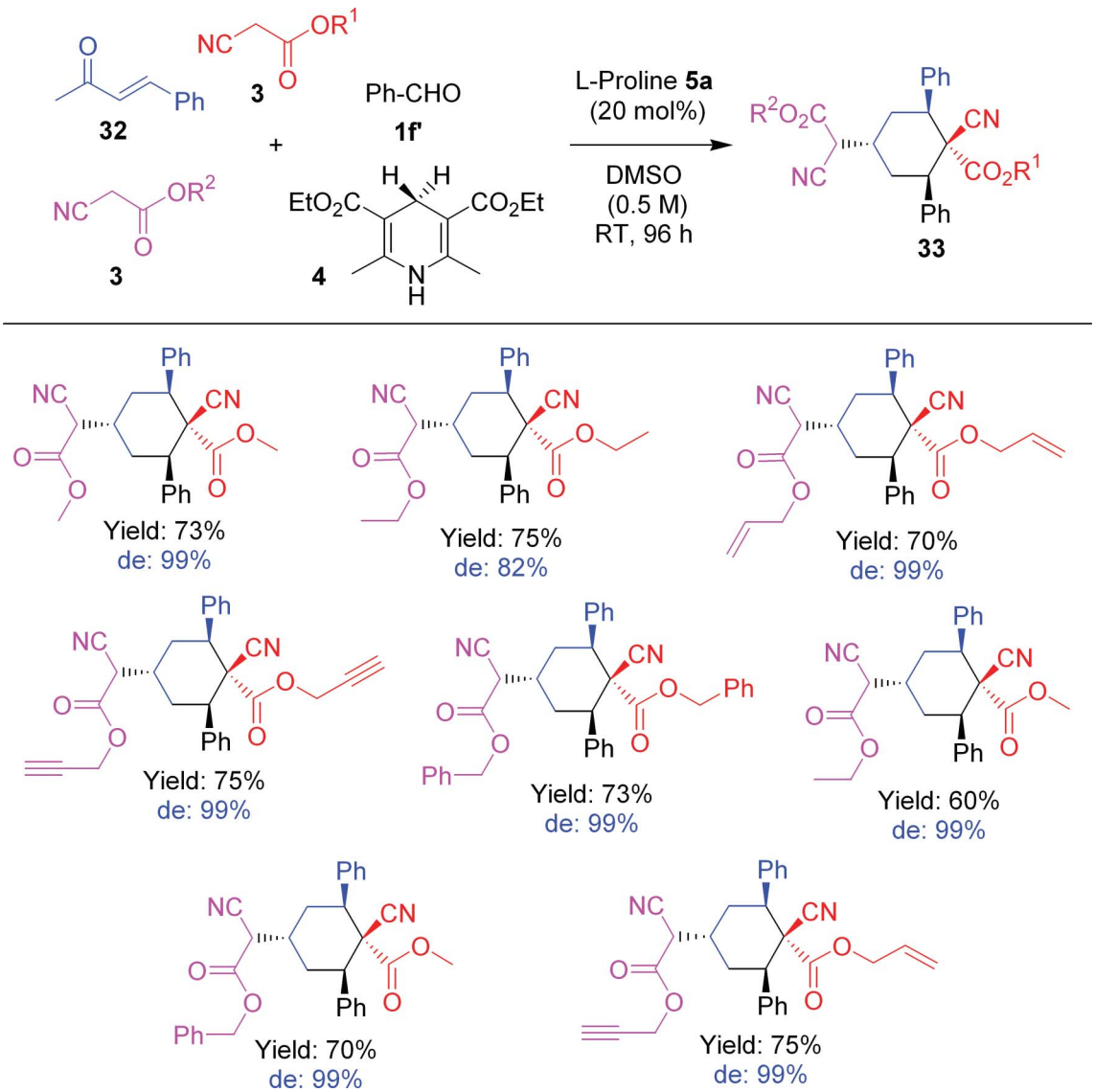
The reaction mechanism for the aniline-, self-, *p*TSA- and K_2CO_3-catalyzed chemoselective synthesis of cascade products **8**, **25** and **27** through reaction of cyclopentane-1,3-dione **3i**, 2-hydroxybenzaldehydes **1**, Hantzsch ester **4** and diazomethane is illustrated in Scheme 13.[16] This catalytic sequential one-pot, double cascade was a four component reaction comprising a cyclopentane-1,3-dione **3i**, 2-hydroxy-benzaldehydes **1**, Hantzsch ester **4**, diazomethane and a simple catalyst, aniline **5d**. In the first step, the catalyst **5d** activates component **1** by imine formation, which then adds to the cyclopentane-1,3-dione **3i** *via* a Mannich and amine-elimination type reaction to generate active olefin **6** (**28** → **29** → **6**). The following second step is biomimetic hydrogenation of active olefin **6** by Hantzsch ester **4** to produce **8** through self-catalysis by decreasing HOMO–LUMO energy gap between **4** and **6** respectively. Highly chemoselective synthesis of cascade hydrogenated products **8** over the bis-adduct **19** formation from reactants **1**, **3** and **4** can be explained by using HOMO–LUMO energy gaps and enthalpy differences of reactants and products.[13b] In the subsequent third step, acid-catalyzed oxy-Michael/dehydration of **8** *via* intermediate **30** leads to the formation of product **27**. In the alternative fourth step, self-catalyzed reaction of **8** with diazomethane leads to the formation of **25**, which on treatment with K_2CO_3 generates the expected one-pot product **27** *via* intermediate **31** as shown in Scheme 13.

Sequential combination of TCRA with olefination, Diels–Alder, and epimerization reactions in one-pot

Highly functionalized cyclohexanes **33** are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products,[17] and also these compounds could serve as suitable synthons for the synthesis of useful materials with different properties. With these applications in mind,



Scheme 13 Proposed catalytic cycle for the sequential combination of MCRs/MCC reactions.



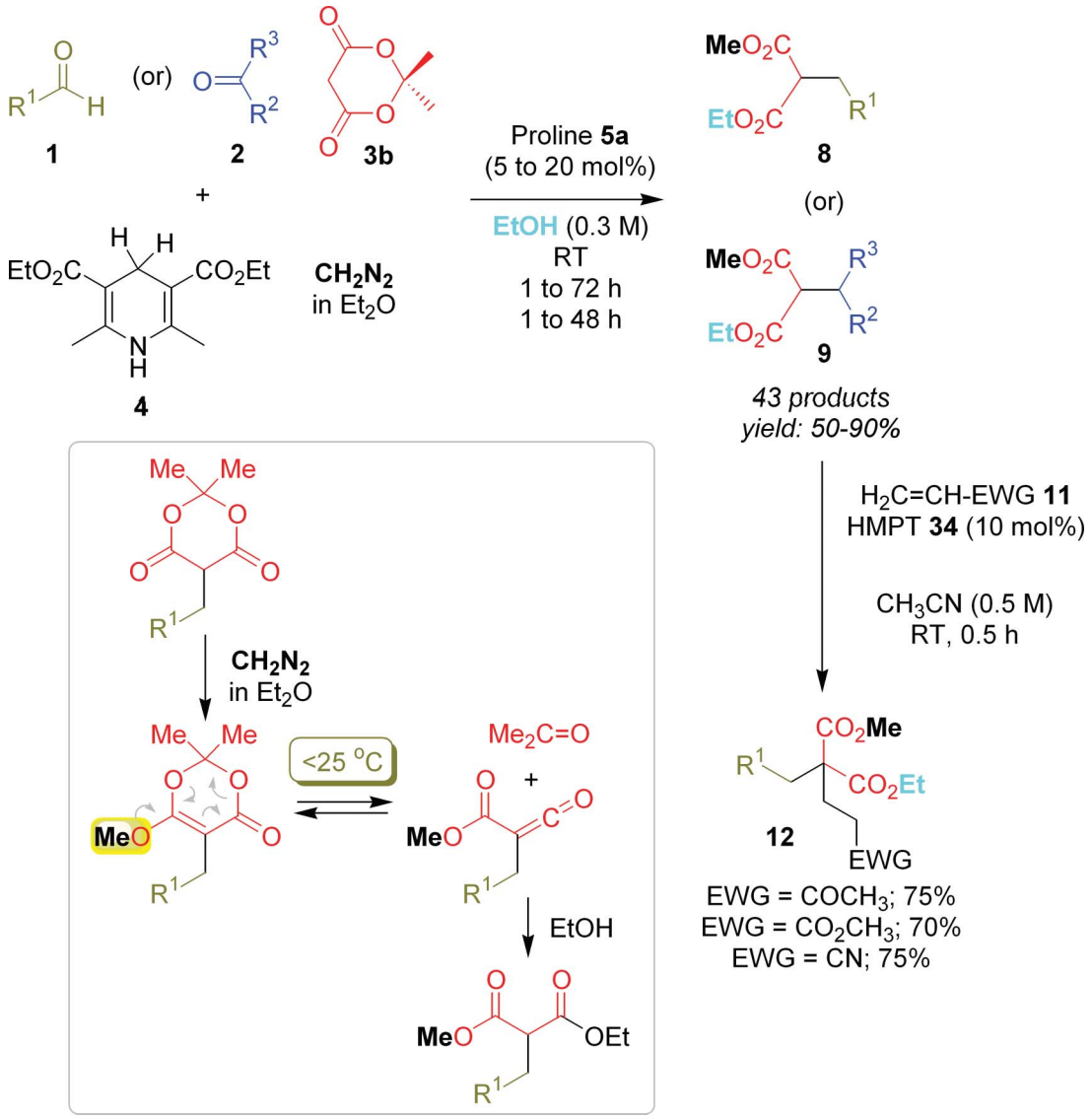
Scheme 14 Sequential combination of five reactions in one-pot.

recently we developed a novel double cascade proline-catalyzed five-component olefination/Diels–Alder/epimerization/TCRA (O/DA/E/TCRA) reaction of enones **32**, aldehydes **1**, CH-acids **3**, and Hantzsch ester **4** with various CH-acids **3** in one-pot (Scheme 14).[17] A library of double cascade products **33** was furnished in good yield with 99% de under proline-catalysis at 25° C for 96 h. This chemistry is an ideal example of the successful application of proline as a dual catalyst for the imine and enamine activation of aldehydes and enones respectively as shown in Scheme 14.

Sequential combination of TCRA with *O*-alkylation, ketenization, esterification, and alkylation reactions in one-pot

2-Alkylmalonates **8**/**9** are an important class of compounds, which display a very large spectrum of biological applications and are widely used as intermediates in pharmaceuticals and agrochemicals.[18] The conventional method to synthesise 2-alkylmalonates is the alkylation of symmetrical malonates with alkyl halides under dry conditions, which has less scope with respect to yields, diverse library generation, and experimental simplicity.

In 2009, as part of our research program to engineer direct MCC reactions based on TCRA platform,[19] we have discovered a metal-free, novel and sustainable technology for the synthesis of highly substituted nonsymmetrical 2-alkylmalonates **8**/**9** and 2,2-dialkylmalonates **12** by using organocatalytic cascade five-component TCRA/alkylation/ketenization/esterification (TCRA/A/K/E) and six-component TCRA/alkylation/ketenization/esterification/alkylation (TCRA/A/K/E/A) reactions of aldehydes **1** or ketones **2**, Meldrum's acid **3b**, Hantzsch ester **4**, diazomethane, alcohols and active ethylene/acetylenes **11** *via* iminium-, self-, self-, self- and base-catalysis in one-pot (Scheme 15).[19] In this work, for the first time we discovered the *in situ* generation of new reactive species of alkyloxycarbonylketenes as key intermediates from TCRA products to generate the library of nonsymmetrical 2-alkylmalonates with good yields *via in situ* generation, cycloreversion and alcohol



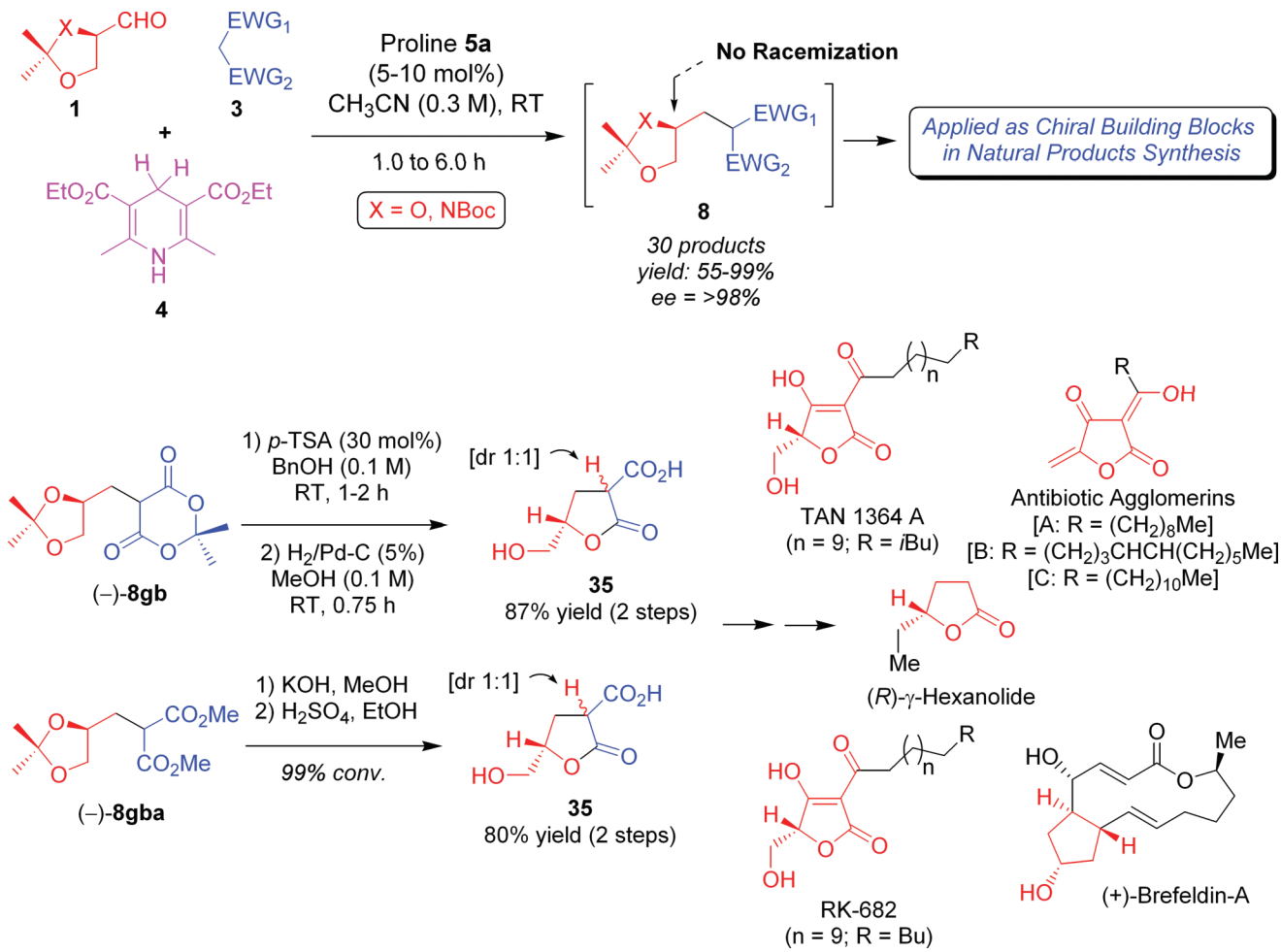
Scheme 15 Sequential combination of MCRs/MCC reactions in one-pot.

addition in one-pot at the ambient conditions as shown in Scheme 15.

High-yielding synthesis of chiral building blocks *via* TCRA for natural products synthesis: formal total synthesis of HIV-1 protease inhibitors, phospholipase A2 inhibitors, antibiotic agglomerins, brefeldin A and (*R*)-γ-hexanolide

After successful demonstration of TCRA reaction with achiral aldehydes and ketones, recently we have explored the potential ability of the chiral aldehydes **1** to participate in an amino acid-catalyzed TCRA reaction with a variety of CH-acids **3** and Hantzsch ester **4** (Scheme 16).[20] We imagined that the reaction of (*R*)-glyceraldehyde acetonide **1g** (>98% ee) with Meldrum's acid **3b** and Hantzsch ester **4** under L-proline-catalysis might lead to racemic 5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl[1,3]dioxane-4,6-dione **8gb**. However, TCRA product **8gb** did not racemize and instead it showed >98% ee under the standard reaction conditions. This unexpected result represents a novel methodology for the preparation of chiral TCRA products and gave inspiration to synthesize a variety of chiral TCRA products in 55–99% yields with >98% ee as shown in Scheme 16.[20]

To test the generality of TCRA reactions, we further synthesized chiral building blocks for natural products synthesis from TCRA products as shown in Scheme 16. Recently chiral (5*S*)-5-hydroxymethyl-2-oxotetrahydrofuran-3-carboxylic acid **35** was used as a key intermediate for the total synthesis of HIV-1 protease inhibitors, phospholipase A_2 inhibitors, antibiotic agglomerins, (*R*)-γ-hexanolide and (+)-brefeldin-A as shown in Scheme 16.[20] S. Ohta *et al.* and T. Kitahara *et al.* prepared the key intermediate **35** in 6 steps starting from (*R*)-glyceraldehyde acetonide **1g** with an overall yield of 40% for their total synthesis.[21] In our recent work, by the combination of cascade TCRA and cascade hydrolysis/lactonization/esterification (H/L/E) reactions, we prepared the key intermediate of chiral acid (5*S*)-**35** by using only 3 synthetic steps (TCRA, H/L/E and hydrogenation) with an overall yield of



Scheme 16 High-yielding synthesis of chiral building block **35** based on TCRA platform and formal synthesis of natural products.

83% with >98% ee as shown in Scheme 16. We also developed another alternative method to prepare (5*S*)-**35** with an overall yield of 60% with >98% ee by using again 3 synthetic steps [TCRA/A/K/E, hydrolysis (H) and lactonization (L)], which is similar to the previous approach for cyclization.

Rapid two-step synthesis of drug-like polycyclic substances by sequential MCC reactions based on TCRA platform

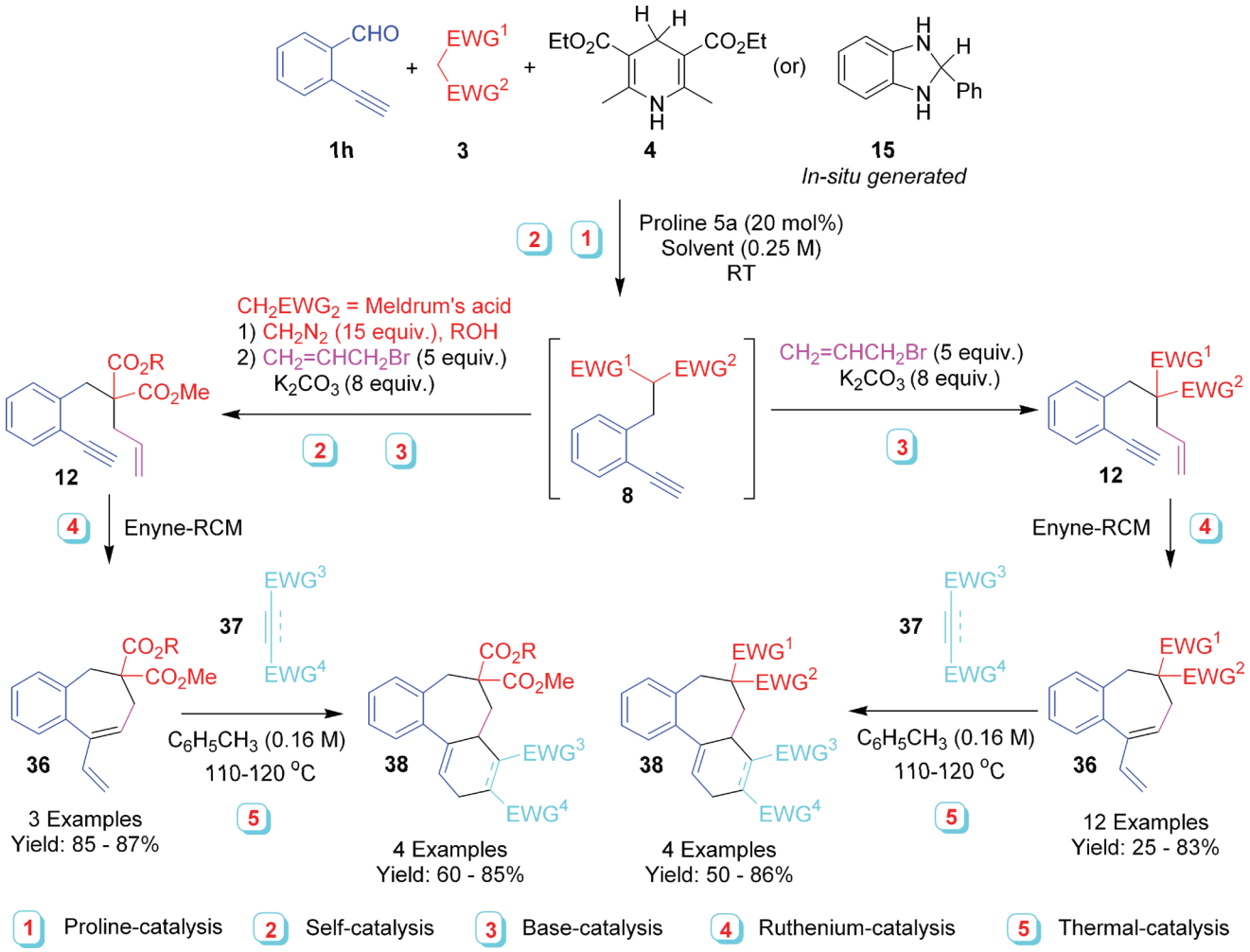
In a continuation of testing the generality of TCRA reaction, recently an efficient amino acid-/self-/base-/ruthenium-/thermal-catalyzed two-step process for the synthesis of drug-like carbocycles **38** was achieved through combinations of cascade TCRA/*C*-allylation/enyne-RCM/Diels–Alder (TCRA/C-A/enyne-RCM/DA) reactions as key steps starting from simple acyclic substrates (Scheme 17).[22]

In 2010, we discovered a novel technology through combination of organocatalysis with ruthenium-catalysis for the two-step synthesis of drug-like carbocycles **36** and **38** using proline-/self-/potassium carbonate-/ruthenium-/thermal-catalysis through cascade TCRA, *C*-A, enyne-RCM and DA reactions as key steps starting from commercially available 2-ethynylbenzaldehyde **1h**, CH-acids **3**, organic-hydrides **4** or **15**, allyl bromide, diazomethane, reactive dienophiles **37**, L-proline **5a**, K_2CO_3 and Grubbs 1st or 2nd generation ruthenium catalysts, an approach we called the "MCC approach to carbocycles" (Scheme 17).[22] This work highlighted the value of TCRA reactions in developing a new synthetic strategy to deliver complex carbocycles with minimum synthetic steps.

Rapid synthesis of functionalized indenes, triazoles and glucocorticoid receptor modulators by sequential MCC reactions based on TCRA platform

In a continuation of testing the synthetic applications of TCRA reaction, recently a general process for the synthesis of substituted indenes **39** and 1,2,3-triazoles **40** was achieved for the first time through MCC reaction of 2-ethynylbenzaldehyde **1h**, CH-acids **3**, organic-hydrides **4**/**15** and azides in the presence of a catalytic amount of L-proline/CuI/DIPEA in one-pot (Scheme 18).[23]

A combination of amino acid or amine and suitably ligated coinage metal ion complexes could be identified as multi-catalysts, and that will be ideal synthetic strategy compared to cellular reactions.[24] Recently, for the first time we utilized iminium activation of aldehydes, self-activation of olefins and simultaneous metal ion activation of alkynes combined in a



Scheme 17 Synthesis of drug-like carbocycles *via* a two-step sequence.

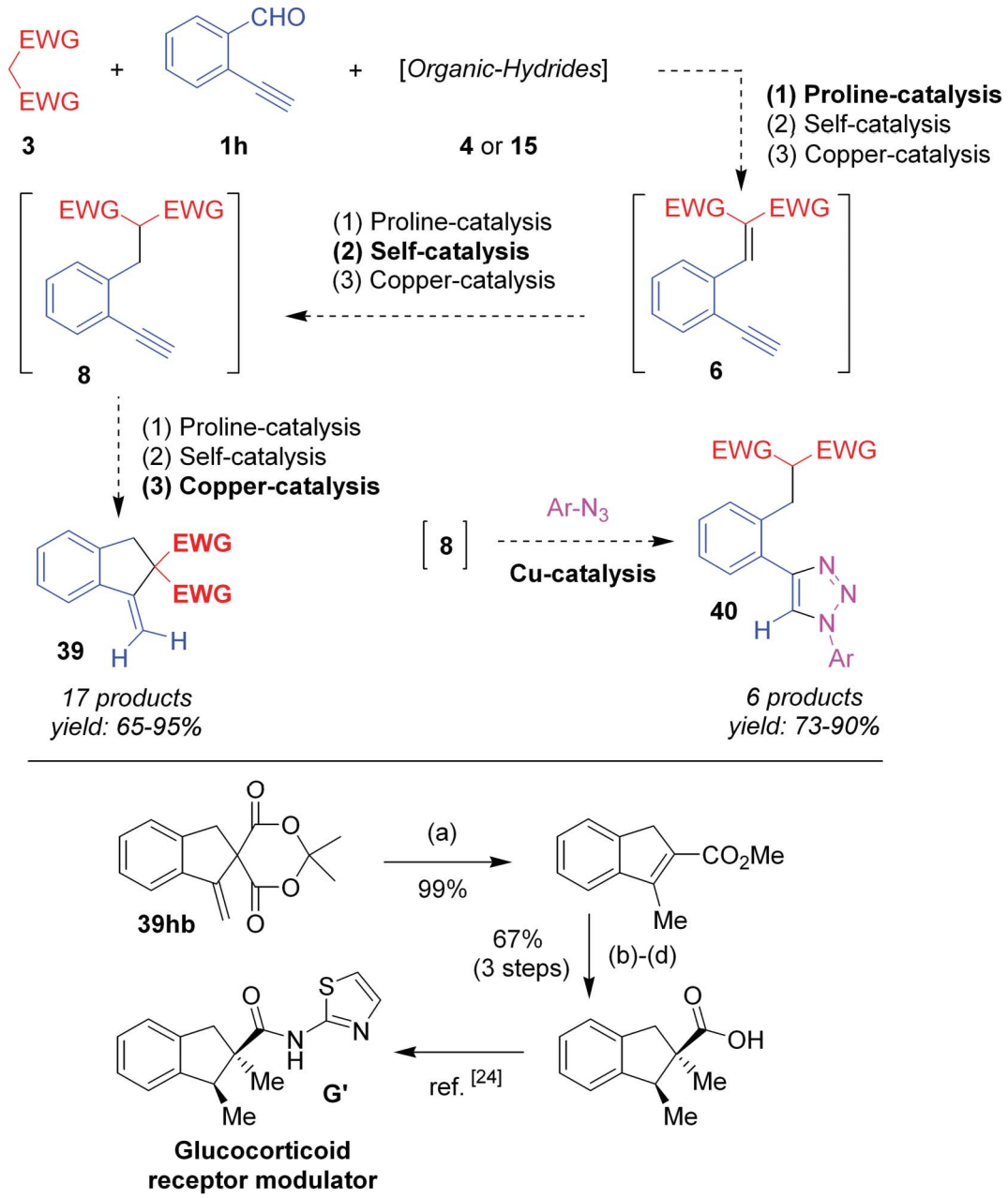
cascade sequence constituting a new carbocyclization method to furnish indenes through Conia-ene reaction and heterocyclization to 1,2,3-triazoles *via* [3+2]-cycloaddition from common substrate and catalyst as shown in Scheme 18. With many points of diversity present in the products, using this MCC process both indene **39** and 1,2,3-triazole **40** libraries were generated in 65–95% yields as shown in Scheme 18. Furthermore, we have given possible support to the existence of dinuclear alkynyl copper(I) complex in click reactions by demonstrating the two kinds of cyclizations on a single substrate **8h**. Many of the achiral building blocks prepared *via* MCC reactions show direct application in pharmaceuticals like glucocorticoid receptor modulator **G′**, which highlights the value of a combination of mild catalysts like amino acid, amines and copper salts in one-pot as shown in Scheme 18.[25]

Application of an organo-click strategy for the cascade synthesis of highly functionalized molecules in one-pot

In a further demonstration of combination of organocatalysis with copper-catalysis in one-pot, a general process for the synthesis of functionalized bis-1,2,3-triazoles **44** was achieved for the first time through the three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions of 2-naphthols **41**, substituted isatins **42** and bis-azides **43** under dimethylamino-ethanol/Cu^{I}-catalysis in one-pot (Scheme 19).[26] Recently we reported that, FCA reaction of **41** and **42** with 5 mol% of dimethylamino-ethanol in CH_2Cl_2 at 25 °C for 8 h furnished the expected FCA adduct in 99% conversion, which on *in situ* treatment with 1,2-bisazidomethylbenzene **43a** in EtOH under $CuSO_4$/Cu-catalysis furnished the expected di[1,2,3]triazole **44a** in 76% yield with formation of one new carbon–carbon σ bond and four new carbon–nitrogen σ bonds in one-pot (Scheme 19).[26] The scope of the dimethylamino-ethanol/Cu^{I}-catalyzed synthesis of compounds of type **44** is revealed by two more examples as shown in Scheme 19. [1,2,3]Triazoles have found wide applications in biology, chemistry, and materials science,[27] thus new one-pot approaches to diverse products are important.

Rapid synthesis of functionalized phenols based on push-pull dienamine platform

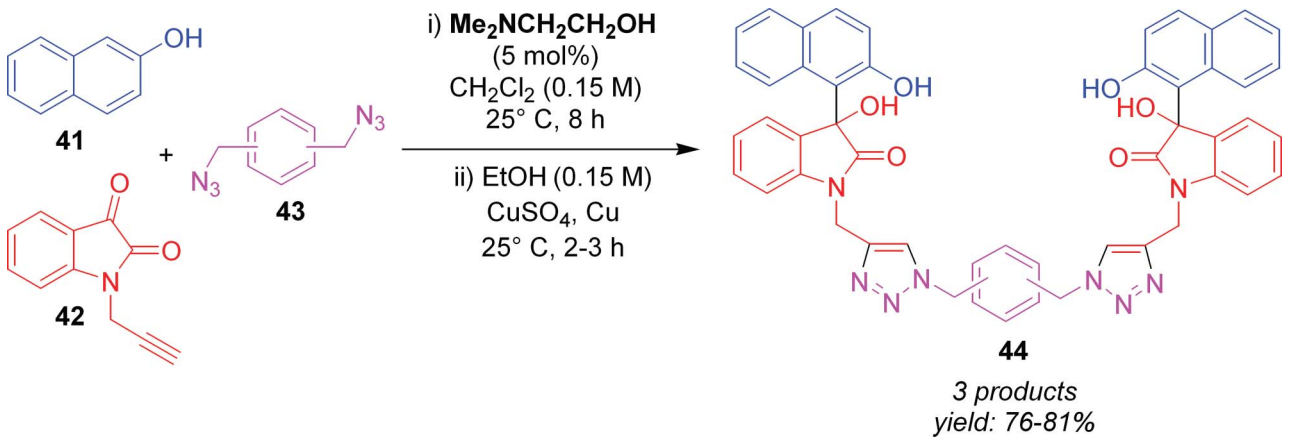
We are very interested in developing ideal new cascade reactions, which should be useful as basic platforms for the development of sequential cascade reactions in one-pot to deliver complex molecules. Keeping this in mind, we developed the novel



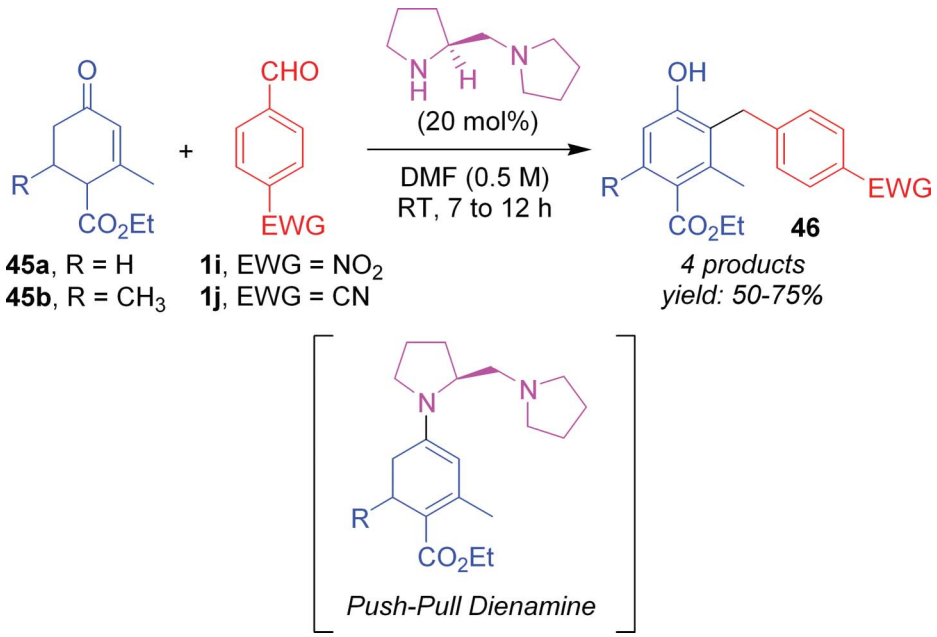
(a) KOH (1 equiv.), MeOH (0.05 M), 65-75 °C, 1 h, 99%; (b) 10% Pd/C (5 mol%), EtOAc (0.1 M), 25 °C, 12 h, 99%; (c) DIPA (2.5 equiv.), nBuLi (2.2 equiv.), MeI (4.5 equiv.), THF (0.25 M), -80 °C, 12 h, 88-90%; (d) 10% aqueous KOH (1 equiv.), MeOH (0.25 M), 100 °C, 12 h, 75%.

Scheme 18 MCC approach to functionalized indenes and triazoles.

Claisen-Schmidt/iso-aromatization (CS/IA) cascade reaction to furnish the functionalized phenols based on the push-pull dienamine (PPD) chemistry (Scheme 20).[28] In 2005, we developed a new, regioselective, one-step, cascade CS/IA reaction of an aldehyde **1** possessing a non-enolizable carbonyl function with highly substituted Hagemann's esters **45** under diamine **5c** catalysis to furnish highly substituted phenols **46** in good yields. The yields and regioselectivities were good. Evidence for a pathway involving *in situ* formation of novel push-pull dienamines from **45** and **5c** was presented along with examples demonstrating the amenability of the process to combinatorial chemistry (Scheme 20).[28] This experimentally simple and environmentally friendly approach can be used to construct highly substituted phenols **46** in a regiospecific fashion. For the first time in organocatalysis, push-pull dienamines were generated *in situ* and shown to be a very good platform for cascade reactions.



Scheme 19 Organo-click approach to functionalized triazoles.



Scheme 20 Direct organocatalytic cascade Claisen–Schmidt/iso-aromatization reactions in one-pot.

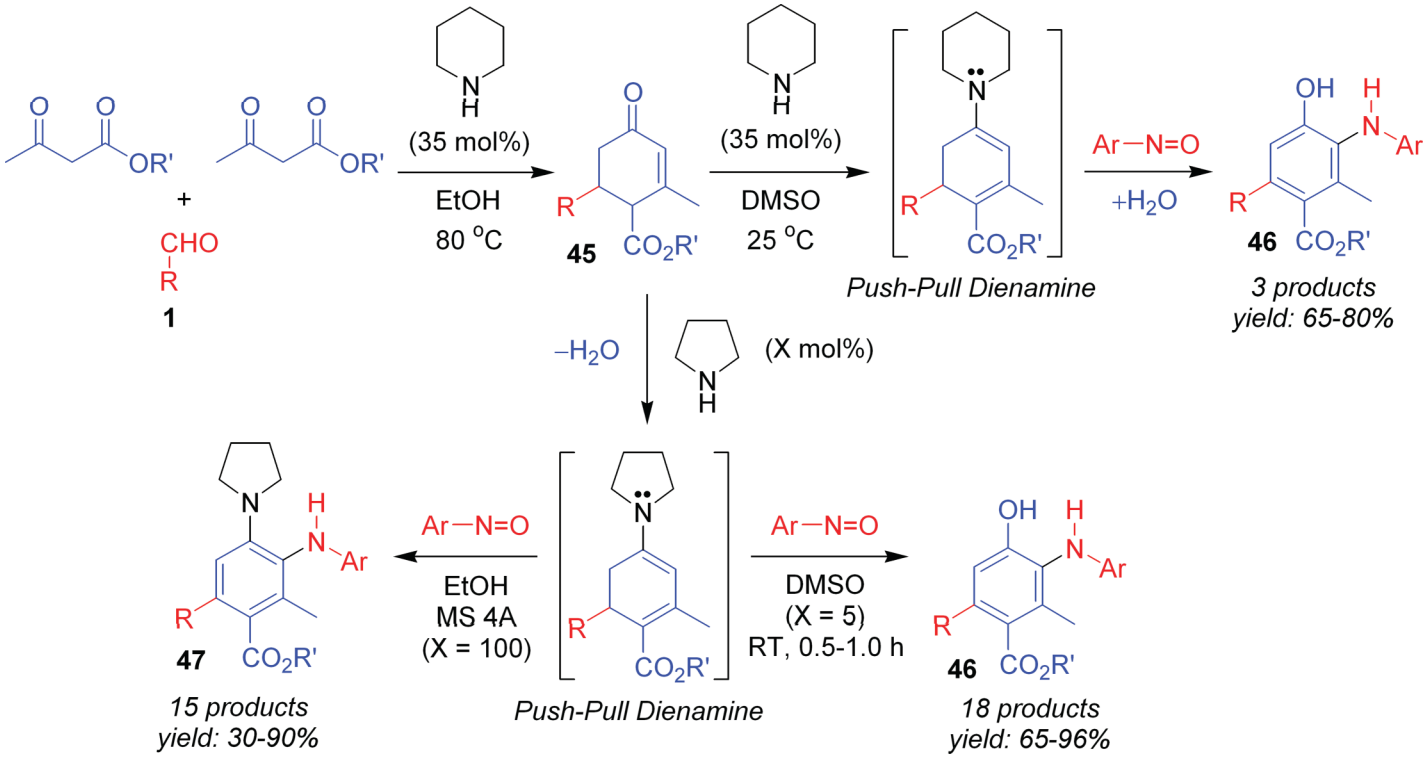
Rapid synthesis of functionalized anilines based on push-pull dienamine platform

In continuation of testing the reactivity of *in situ* generated PPDs, an efficient amine-catalyzed one-pot process for the synthesis of anilines **46** and **47** was achieved through combinations of cascade Knoevenagel/Michael/aldol condensation/decarboxylation (K/M/A/DC) and cascade enamine amination/iso-aromatization (EA/IA) reactions as key steps starting from simple alkyl acetoacetates, aldehydes and nitrosoarenes as substrates (Scheme 21).[29]

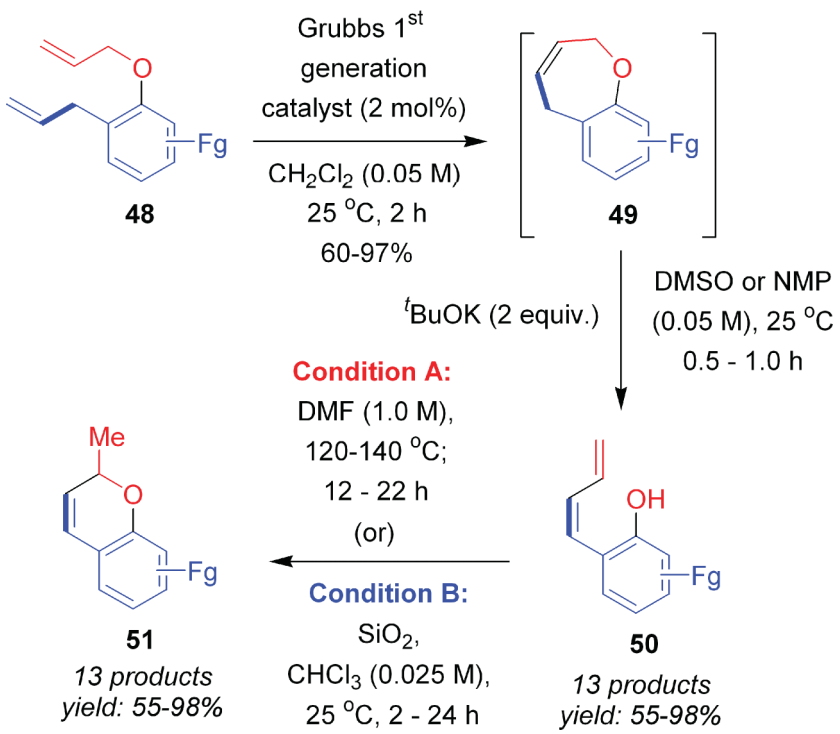
In 2007, we discovered a novel metal-free technology for the single-step synthesis of anilines **46** and **47** with good to excellent yields through sequential combination of six reactions in one-pot by using piperidine- or pyrrolidine-catalysis *via* cascade K/M/A/DC and EA/IA reactions as key steps starting from commercially available alkyl acetoacetates, aldehydes, nitrosoarenes and amines (Scheme 21).[29] This work highlights the value of PPDs as reactive intermediates for the synthesis of functionalized anilines in good yields without metal-catalysts.

One-pot synthetic approach to highly functionalized (*Z*)-2-buta-1,3-dienylphenols and 2-methyl-2*H*-chromenes

Functionalized 2-buta-1,3-dienylphenols **50** and 2-methyl-2*H*-chromenes **51** are of considerable importance in a variety of industries and they are very good building blocks for the synthesis of natural products.[30] In continuation of our aim for the synthesis of complex molecules in one-pot, an efficient [Ru]-, base- and silica-catalyzed one-pot process for the synthesis of (*Z*)-2-buta-1,3-dienylphenols **50** and 2-methyl-2*H*-chromenes **51** was achieved through sequential combination of cascade ring closing metathesis/base induced ring opening/[1,7]-sigmatropic hydrogen shift (RCM/BIRO/[1,7]-SHS) reactions from simple dienes **48** (Scheme 22).[30]

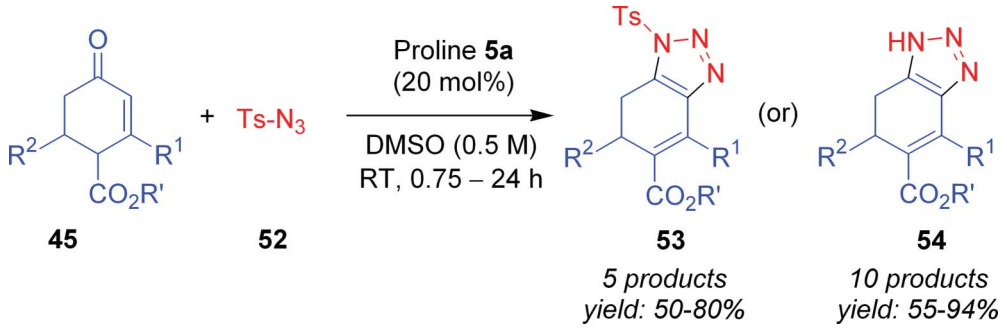


Scheme 21 Direct organocatalytic cascade approach to the synthesis of highly substituted anilines.

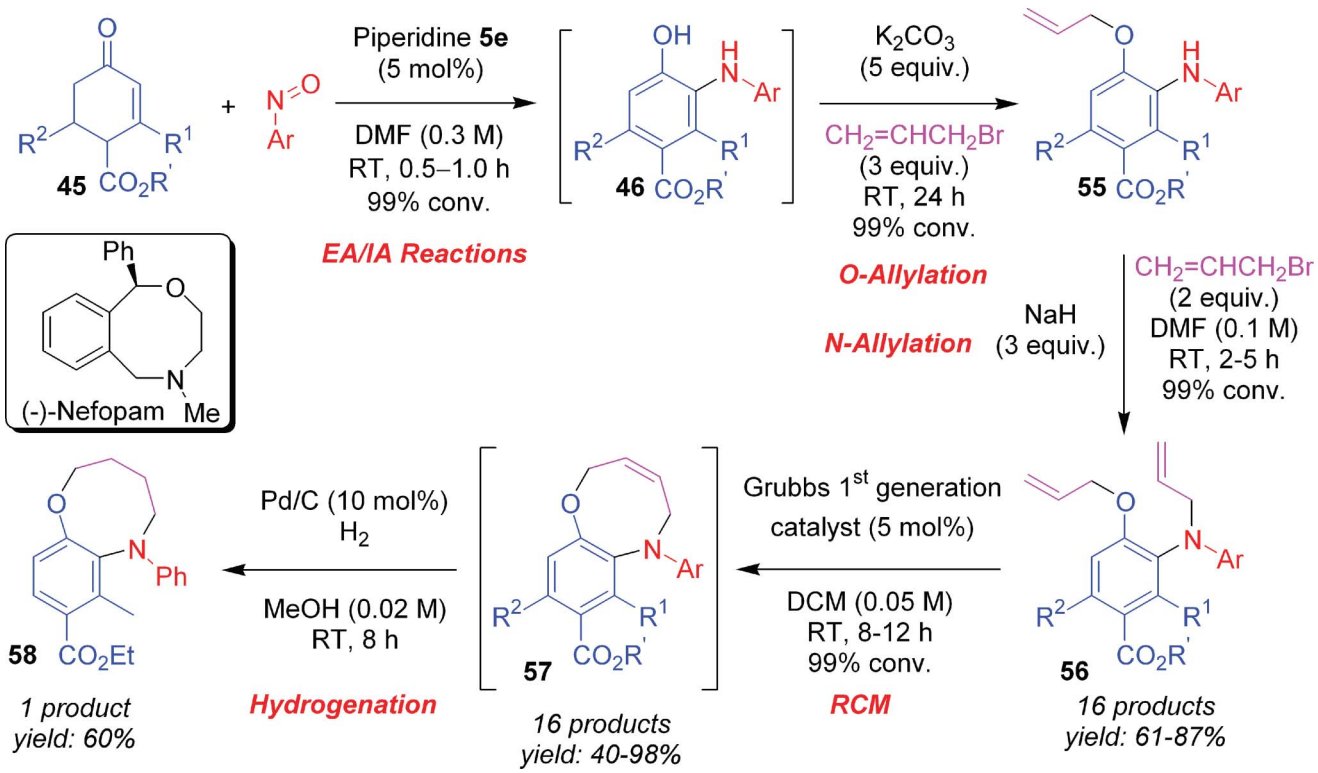


Scheme 22 Sequential one-pot combination of RCM/BIRO/[1,7]-SHS reactions.

In 2008, for the first time we developed a practical and simple one-pot multi-catalysis process for the synthesis of a library of highly substituted (*Z*)-2-buta-1,3-dienylphenols **50** and 2-methyl-2*H*-chromenes **51** in good yields with high selectivity *via* benzo[*b*]oxepines **49** from simple starting materials through RCM/BIRO/[1,7]-SHS reactions as shown in Scheme 22.[30]



Scheme 23 Direct organocatalytic cascade approach to the synthesis of functionalized N*H*-1,2,3-triazoles.



Scheme 24 High-yielding synthesis of Nefopam analogues by sequential one-pot cascade reactions.

Synthesis of functionalized N*H*-1,2,3-triazoles *via* amino acid-catalyzed cascade [3+2]-cycloaddition/hydrolysis reactions based on the push-pull dienamine platform

N*H*-1,2,3-Triazoles are an important class of heterocycles, which display a very large spectrum of biological activities and are widely used as pharmaceuticals and agrochemicals.[27] As such, the development of more general catalytic methods for their preparation is of significant interest. The recent discovery of the novel technology of Cu^{I}-catalyzed [3+2]-cycloaddition reactions of terminal alkynes with azides to provide a general route to a variety of 1,2,3-triazoles in good yields has become a paradigm of a "click chemistry" reaction.[8]

Recently, the copper-catalyzed azide–alkyne click reaction has proven extremely valuable for attaching small molecular probes to various biomolecules in a test tube or on fixed cells.[31] However, its use for biomolecule labeling in live cells or organisms is prohibited by the requirement of a cytotoxic copper catalyst.[31]

In 2008, we discovered a copper-free, novel and green technology for the synthesis of highly substituted *N*H-1,2,3-triazoles by using organocatalytic cascade [3+2]-cycloaddition/hydrolysis ([3+2]-CA/H) reactions from commercially available activated enones **45**, azides **52** and a catalytic amount of proline **5a** (Scheme 23).[32] In this work, for the first time we discovered the organocatalytic approach to the synthesis of *N*H-1,2,3-triazole products **54** in good yields *via* push-pull dienamine chemistry as shown in Scheme 23. Further development of this reaction with different substrates may convert it into a useful bioorthogonal reaction.

High-yielding synthesis of Nefopam analogues by sequential one-pot cascade reactions based on the push-pull dienamine platform

In continuation of demonstrating the applications of PPD chemistry, recently an efficient amine-/ruthenium-catalyzed

three-step process for the synthesis of Nefopam analogues **58** was reported through combinations of cascade enamine amination/iso-aromatization/allylation, *N*-allylation and diene or enyne metathesis as key steps starting from Hagemann's esters **45**. In this work, we discovered the application of ruthenium-catalysis on olefins containing free amines **56** without *in situ* formation of salts (Scheme 24).[33]

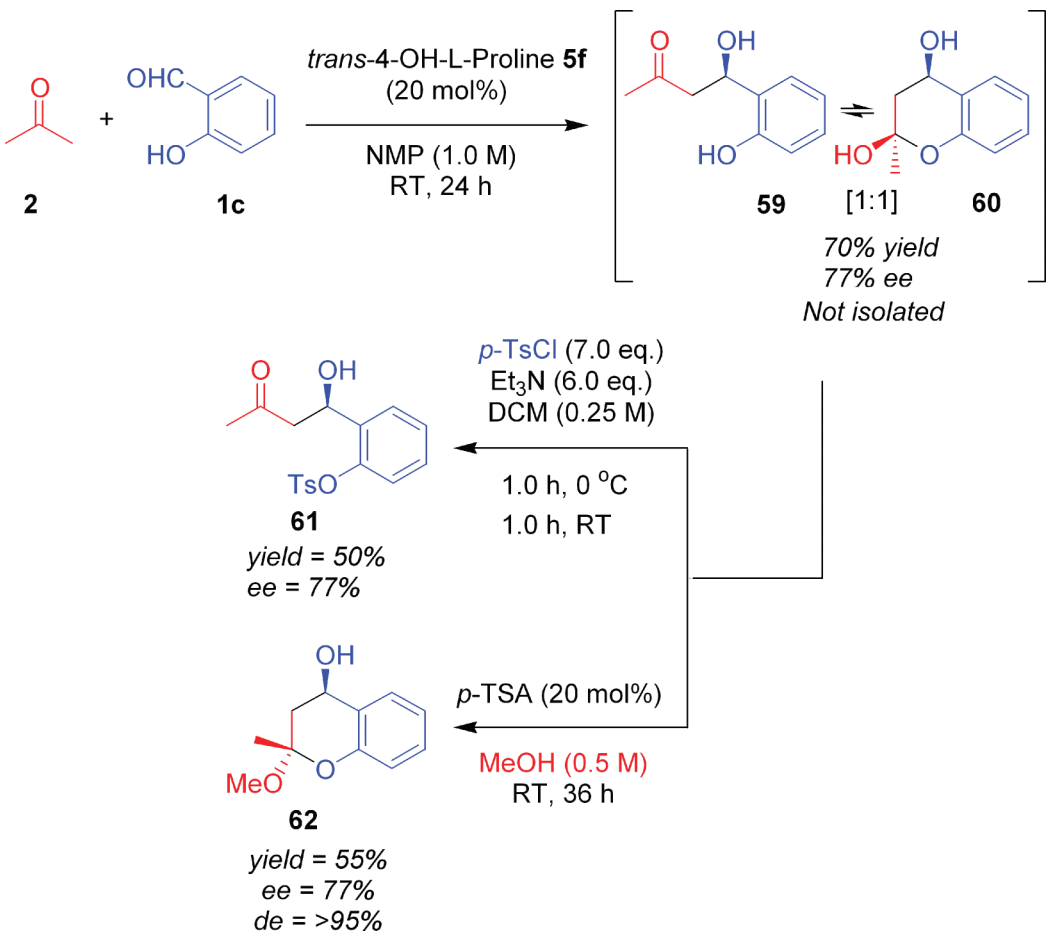
Drug-like highly substituted heterocycles are of considerable importance in a variety of industries. For example functionalized benzoxazocines and pharmaceutically acceptable salts thereof, may be useful as analgesic agents, for the treatment of emesis, depression, post-traumatic stress disorders, attention deficit disorders, obsessive compulsive disorders and sexual dysfunction, and as centrally acting skeletal muscle relaxants.[34] As we are interested to develop drug-like heterocycles in good yields with minimum synthetic steps from PPD reactions, recently we reported for the first time an organocatalytic approach to the high yielding synthesis of functionalized benzoxazocines **57** from a three-step sequence *via* "combination of amine-/ruthenium-catalysis".[33]

In 2009, we discovered a novel and green technology for the three-step synthesis of a library of highly substituted benzoxazocines **57** in good yields using amine/potassium carbonate/sodium hydride/ruthenium-catalysis through cascade enamine amination/iso-aromatization/*O*-allylation (EA/IA/A), *N*-allylation, and diene or enyne metathesis as key steps starting from commercially available Hagemann's esters **45**, nitrosobenzenes, allyl bromide, piperidine **5e** and Grubbs 1st generation ruthenium catalysts, an approach we call "multi-catalysis approach to heterocycles" (Scheme 24). This work highlights the value of PPDs as reactive intermediates for useful chemistry as shown in Scheme 24.

Direct catalytic asymmetric synthesis of functionalized chromans *via* Barbas–List aldol/acetalization reaction

Chromanes and chromenes are an important class of heterocycles, which display a very large spectrum of biological activities and are widely used as drug intermediates and ingredients in pharmaceuticals.[15] In 2009, for the first time we reported the organocatalytic cascade approach to the asymmetric synthesis of functionalized chromans **60** and **62** *via* "Barbas–List aldol/acetalization reactions (BLA/A)" as shown in Scheme 25.[35]

BLA reaction of acetone **2** with 2-hydroxybenzaldehyde **1c** under *trans*-4-OH-L-proline **5f**-catalysis at 25 °C in NMP furnished the aldol↔lactol product (+)-**59**/**60** in 70% yield with 77% ee, which on treatment with *p*-TsCl and Et_3N in one-pot furnished the selectively tosylated product (+)-**61** in 50% yield with 77% ee as shown in Scheme 25. In a similar manner, treatment of reaction intermediate (+)-**59**/**60** with *p*-TSA in MeOH at 25 °C in one-pot furnished the selectively *trans*-2-methoxy-2-methylchroman-4-ol (+)-**62** in 55% yield with 77% ee and >95% de as shown in Scheme 25.



Scheme 25 High-yielding synthesis of chiral chromans *via* BLA/A reactions.

The future of sequential one-pot combination of MCR and MCC reactions

Although the above account touches only the tip of an immense iceberg, it is an indicator of the new spirit, which has emerged with the evocative phrase "bio-inspired chemistry". We have presented the recent research advances in stunning sequential one-pot combination of multi-component and multi-catalysis cascade reactions, which have paved the way for targeting fine chemicals, agrochemicals, pharmaceutical drugs, drug intermediates and ingredients in a single step. This progress has prompted to declare synthetic chemistry going to be a mature field. The goals of synthetic efficiency inherent to the design of cost effective transformations have long been embraced by chemists and represent an inevitable consequence of a fiscal as well as artistic natural selection processes. Therefore, a combination of MCR/MCC reaction seems a more likely successful scenario and more optimistic reports are inclined to view.

Abbreviations and acronyms used in this article

Multi-component Reaction	(MCR)
Multi-catalysis Cascade	(MCC)
Three-component Reductive Alkylation	(TCRA)
Push-pull Dienamine	(PPD)
Highest Occupied Molecular Orbital	(HOMO)
Lowest Unoccupied Molecular Orbital	(LUMO)
Three-component Reductive Alkylation/Hydrolysis	(TCRA/H)
Three-component Reductive Alkylation/Alkylation	(TCRA/A)
Steric Strain Control	(SSC)
Product Stability Control	(PSC)
Olefination/Hydrogenation	(O/H)
Olefination/Hydrogenation/Alkylation	(O/H/A)
Olefination/Hydrogenation/Alkylation/Huisgen Cycloaddition	(O/H/A/HC)
Wieland–Miescher	(W–M)
Hajos–Parrish	(H–P)
Robinson Annulation	(RA)
Three-component Reductive Alkylation/Robinson Annulation	(TCRA/RA)
Three-component Reductive Alkylation/Oxy-Michael/Dehydration	(TCRA/OM/DH)
Three-component Reductive Alkylation/Alkylation/Oxy-Michael/Dehydration	(TCRA/A/OM/DH)
Alkylation/Oxy-Michael/Dehydration	(A/OM/DH)
Olefination/Diels–Alder/Epimerization/Three-component Reductive Alkylation	(O/DA/E/TCRA)
Three-component Reductive Alkylation/Alkylation/Ketenization/Esterification	(TCRA/A/K/E)
Three-component Reductive Alkylation/Alkylation/Ketenization/Esterification/Alkylation	(TCRA/A/K/E/A)
Hydrolysis/Lactonization/Esterification	(H/L/E)
Three-component Reductive Alkylation/*C*-Allylation/Enyne-RCM/Diels–Alder	(TCRA/C-A/enyne-RCM/DA)
Friedel–Crafts Alkylation/Huisgen Cycloaddition	(FCA/HC)
Claisen–Schmidt/Iso-aromatization	(CS/IA)
Knoevenagel/Michael/Aldol condensation/Decarboxylation	(K/M/A/DC)
Enamine Amination/Iso-aromatization	(EA/IA)
Enamine Amination/Iso-aromatization/*O*-Allylation	(EA/IA/A)
Ring Closing Metathesis/Base-Induced Ring Opening	(RCM/BIRO)
[1,7]-Sigmatropic Hydrogen Shift	([1,7]-SHS)
[3+2]-Cycloaddition/Hydrolysis	([3+2]-CA/H)
Barbas–List Aldol/Acetalization	(BLA/A)

Acknowledgements

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