Conference paper

Armando Córdova*

Combined heterogeneous metal/organic catalysts for eco-friendly synthesis

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Abstract: The interplay and synergistic cooperation between homogeneous and heterogeneous catalyst systems is of utmost importance in nature. It is also applied in chemical synthesis. Here, it can allow for new reactivity, which is not possible by the employment of a single catalyst, and promote the catalysis of multiple transformations in a one-pot sequence. This could overall lead to novel reactions and the development of sustainable chemistry. In this context, a versatile and broad synergistic strategy for the selective synthesis of valuable molecules with variable complexity and under eco-friendly conditions is disclosed. It is based on integrated heterogeneous metal/organo multiple relay catalysis, which is performed in a single reaction vessel, and allows for the assembly of complex molecules (e.g., heterocycles and carbocycles) with up to three quaternary stereocenters in a highly enantioselective fashion from simple alcohols and air/O_2.

Keywords: aerobic oxidations; asymmetric synthesis; biomaterials; biomimetic; biomimetic synthesis; carbocycles; cascade reactions; chemistry; eco-friendly synthesis; green chemistry; NICE-2014; selectivity.

Introduction

In nature, well-organized multi-enzymatic systems of the cell perform efficient and selective asymmetric relay catalysis (ACR) via specific biochemical pathways for simple achiral and chiral molecules [1]. Remarkably, these ARC domino/cascade sequences can also accomplish precise and economic synthesis of complex molecules such as carbocycles (monoterpenes, taxanes, etc.) and heterocycles (sugars, alkaloids, etc.) with excellent enantioselectivity [2–4]. Contrary to this efficient strategy, organic synthesis generally operates via stepwise reactions where isolation and purification of key intermediates are often required for success in further transformations [5]. Each pillar of catalysis (i.e., metal catalysis, organocatalysis, and biocatalysis) has its own advantages, limitations, and range of applications. However, when merging them in order to mimic and rival the biosynthesis serious issues such as inactivation or side-reactions can occur [6–9]. Ways of avoiding these problems would be to perform the catalysis in sequential steps and/or site isolation of catalyst (e.g., immobilization, heterogeneous or biphasic reaction conditions) [10–12]. This would also allow for mediating multiple transformations in a single transformation event under green chemistry conditions [13, 14].

The development of asymmetric relay catalysis (ARC), which combines organic and homogeneous metal catalysts [9, 15–23], has attracted considerable attention in recent years. It allows for novel reactivity, which

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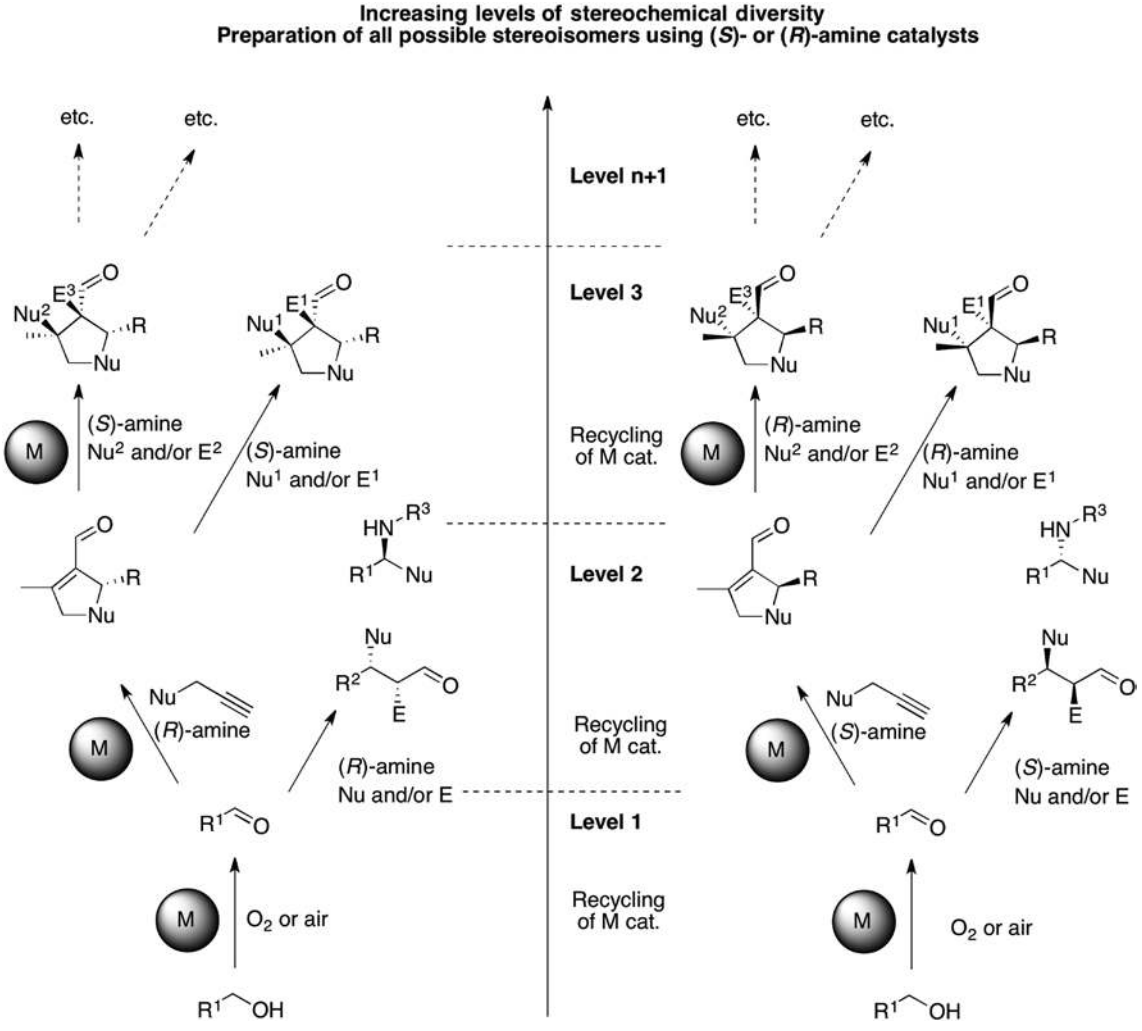
***Corresponding author: Armando Córdova,** Department of Natural Sciences and Fibre Science and Communication Network, Mid Sweden University, Holmgatan 10, 85170 Sundsvall, Sweden; and Berzelii Centre EXSELENT on Porous Materials, Stockholm University, 10691 Stockholm, Sweden, e-mail: armando.cordova@miun.se

cannot be accomplished employing the catalysts separately. A new and important way of accomplishing ARC would be to introduce homogeneous and heterogeneous catalyst systems, which operate in synergy. Here the heterogeneous catalysis part would allow for reactivity not possible using the homogeneous organometallic catalyst (e.g., both reduction and oxidation cascade reactions), as well as facile separation and recycling of the non- environmentally friendly and expensive transition metal. Thus, we envisioned a novel highly selective ARC strategy based on combining the paradigms of heterogeneous transition metal catalysis with organocatalysis for the production of designed chiral molecules in a single purification step and under eco-friendly conditions (Scheme 1). The challenge of creating molecules with multiple and quaternary stereocenters in a highly stereoselective fashion should also be met by this tactic [24–26]. The underpinning of our strategy is the intrinsic ability of a heterogeneous metal catalyst to take part in several cascade sequences and cooperate with small chiral amine catalysts and substrate additives during this ARC.

Results and discussion

Recently, the concept of merging metal catalysis and organocatalysis in one-pot ("metal/organo cooperative catalysis") has grown [15–23, 27–47]. Here we have discovered that transition metal catalysis could be



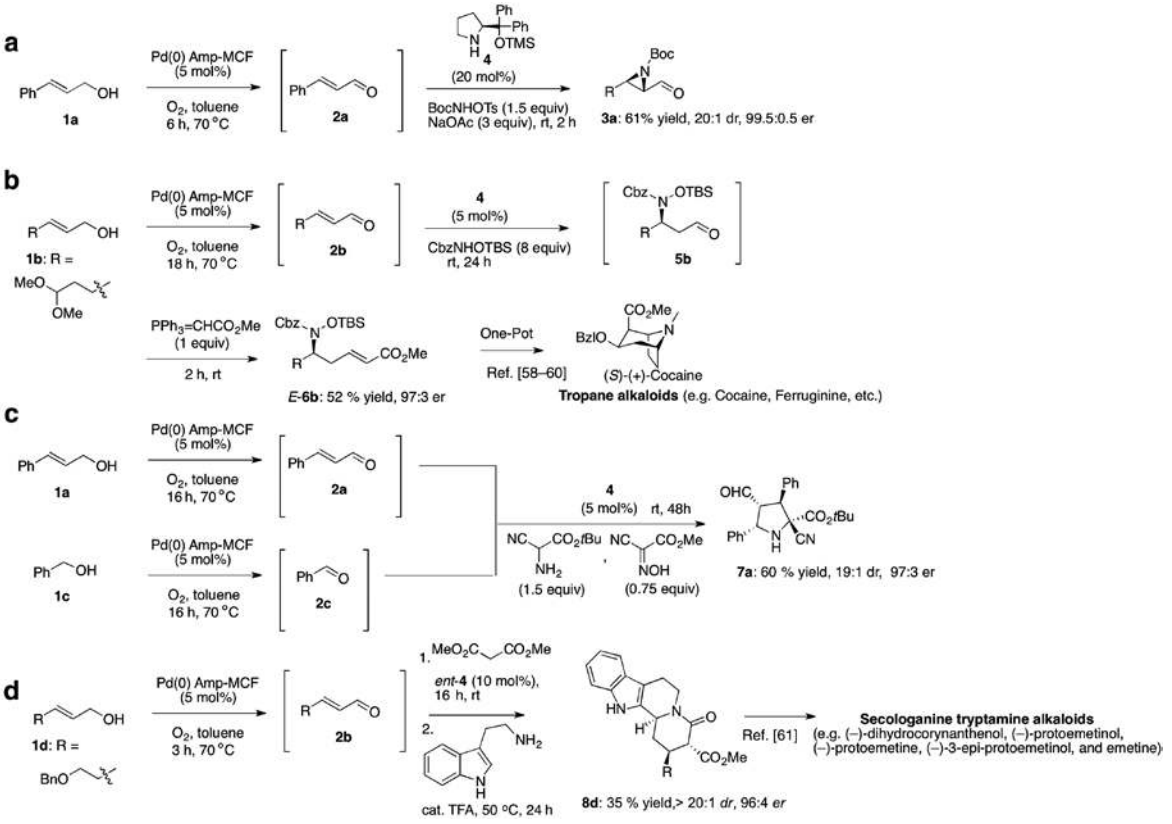
Scheme 1: Combined heterogeneous metal/chiral amine relay catalysis strategy. Nu = Nucleophile, E = electrophile.

combined with aminocatalysis and thereby accomplish single and multiple C–C, C–Si, C–O, C–N, C–B bond-forming reactions in one-pot [15, 16, 27–33]. This synergistic interplay between metals, organic ligands and chiral amines leads to unique reactivity under homogeneous reaction conditions. Among the reactions explored, we had developed an allylic alcohol oxidation/Michael/ carbocyclization catalytic relay using a bench-stable palladium complex ($Pd(PPh_3)_4$) and a simple chiral amine with molecular oxygen as the terminal oxidant [48]. Palladium is a powerful and versatile transition metal, which can be immobilized on various solid supports and next be used as a heterogeneous catalyst for efficient chemical reactions [49–56]. In this context, we recently disclosed that enantioselective carbocyclizations could be performed by the synergistic action of a heterogeneous palladium catalyst and a chiral amine co-catalyst [57]. The above results in metal/organo cooperative catalysis inspired us to design and explore the multicatalysis relay strategy using palladium nanoparticles as the heterogeneous catalysts and the aerobic oxidation of alcohols to aldehydes as the initial entry transformation (Scheme 1, level 1). Next, these aldehydes could be further selectively transformed by organocatalysis to a plethora of valuable molecules in a precise stereochemical way followed by recycling of the heterogeneous metal catalysts (Scheme 1, level 2). However, in order for these ARC sequences to be possible and thereby reach the full potential of aminocatalytic reactions [58–60], the heterogeneous metal catalyst should not obstruct the subsequent steps or be inhibited. The ARC sequences of the proposed heterogeneous metal/organo cooperative catalysis strategy could be further expended by linking it with for example synergistic metal/chiral amine co-catalyzed stereoselective Michael/carbocyclization cascade transformations (Scheme 1, level 2). Further manipulation of the products from this tactic could take part in additional relay sequences as described above expanding the stereochemical space in a controlled fashion using different enantiomers of the amine catalyst (Scheme 1, level 3). Thus, the stereochemical complexity of this ARC strategy increases.

At the onset of our studies, we investigated different approaches for implementing various organocatalytic transformations with the ARC strategy at level 2 as depicted in Scheme 1. A broad range of ARC sequences including organocatalytic cascade and multi-component reactions were developed starting from different allylic or benzylic alcohols (Scheme 2).

Thus, the palladium (0)-aminopropyl-mesocellular foam (Pd(0)-AmP-MCF)-catalyzed aerobic oxidation [31] of alcohols **1** was linked in sequence with several chiral amine **4** [61]-catalyzed one-pot cascade transformations and provided a variety of functional molecules (e.g., aziridine **3a** [62, 63], *E*-**6b** [64, 65], pyrrolidine **7a** [66] and **8d** [67]) with high enantiomeric ratios (Scheme 2). Next, these compounds such as *E*-**6b** and **8d** can be rapidly converted to tropane alkaloids (e.g., cocaine) [64, 65] and secologanine tryptamine alkaloids [67], respectively (Scheme 2b and 2d). An aerobic oxidation/Michael/ carbocyclization cascade sequence employing the combined heterogeneous Pd/chiral amine multiple relay catalysis and molecular oxygen/air as the terminal oxidant was also investigated (Scheme 3). Different Pd(0)-catalysts were used for the ARC [48, 57, 68]. Here the catalysts systems with Pd(0)-AmP-MCF or Pd(0)-aminopropyl-controlled pore glass (Pd(0)-AmP-CPG) as the co-catalyst exhibited a broad substrate scope and delivered various carbocycles **10**, heterocycles **11** and **12** with high ers [69–71]. Here Pd(0)-AmP-CPG was the most efficient co-catalyst for this relay sequence. In comparison, the homogeneous $Pd(0)(PPh_3)_4$/chiral amine catalyst system was also highly selective but exhibited a more narrow substrate scope.

After probing level 2, we began to explore the possibility of reaching higher levels of complexity and constructing vicinal quaternary stereocenters by expanding the combined heterogeneous metal/chiral amine concept to level 3 (Scheme 1). As a proof of concept of this tactic, we planned an aerobic oxidation/Michael/carbocyclization/aziridination cascade reaction via carbocycles **10** to aziridine **13** with three quaternary stereocenters. It is noteworthy that this potential catalytic asymmetric relay need to achieve two sequential highly stereoselective domino reactions after the initial catalytic aerobic oxidation of **1**. However, the chiral amine-catalyzed direct aziridination step of **10** with a sterically hindered enal moiety looked very difficult. The catalytic one-pot reaction was first investigated using chiral amine **4** as the co-catalyst (Scheme 4). However, the ARC stopped at level 2 and only carbocycle **10** was assembled. This result prompts us to investigate the catalytic aziridination of enal **10** using **4**, *ent*-**4** and racemic **4** as catalysts, respectively. To our delight, we found that *ent*-**4** and racemic **4** were able to convert **10a–13a** while **4** did not catalyze the reaction. Therefore the

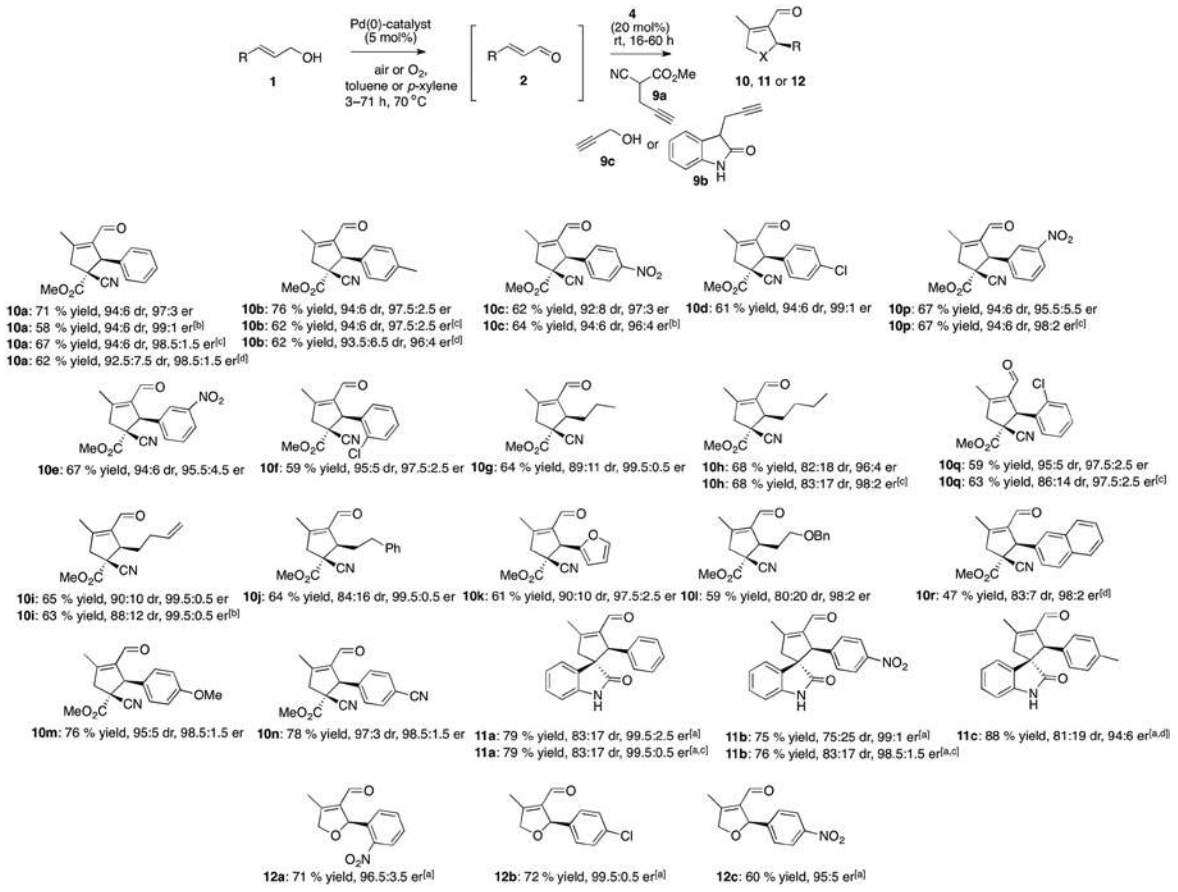


Scheme 2: Examples of ARC at level 2. Cbz = Benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

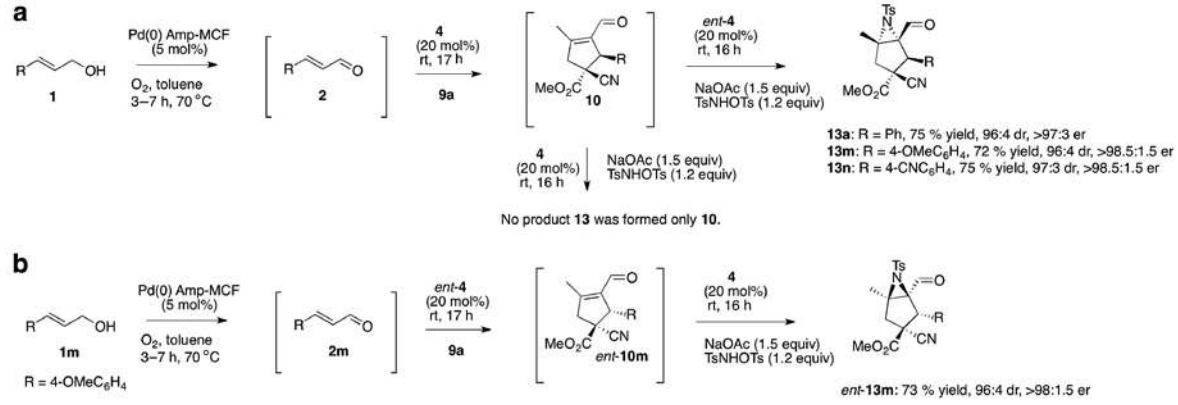
catalytic aerobic oxidation/Michael/carbocyclization/aziridination relay sequence was first performed with addition of **4** prior to the Michael/carbocyclization domino transformation and then adding an equal amount of *ent*-**4** to the reaction mixture prior to the final aziridination step. Thus, the last step of this one-pot ARC sequence was performed with a racemic catalyst **4** but only the (*R*)-enantiomer (*ent*-**4**) catalyzed the final transformation. With these results in hand, a set of polysubstituted aziridines **13** (up to 97:3 and >98.5:1.5 er), bearing three quaternary stereocenters were prepared in one-pot. Moreover, starting the ARC sequence with *ent*-**4** as the catalyst and **1m** as the allylic alcohol afforded *ent*-**13m** in high yield, dr and er. Future investigations would include kinetic resolution of racemic compounds **10** by the chiral amine **4** catalyzed azirdinarion transformation [62, 63].

An important aspect of using a heterogeneous catalyst with immobilized palladium nanoparticles is that it can be employed for both aerobic oxidation and hydrogenation transformations. This feature inspired us to investigate a catalytic aerobic oxidation/Michael/carbocyclization/hydrogenation relay using a chiral amine/heterogeneous palladium catalyst system and molecular oxygen as the "green" oxidant (Scheme 5a).

Next, the ARC sequence was performed and H_2 was connected to the reaction flask as soon as full conversion of **2–10** had been completed. Moreover, the reaction rate was accelerated by increasing the temperature to 60 °C. Gratifyingly, the reaction was 1,4-regiospecific and highly enantioselective and polysubstituted carbocycles **14a** (73:27 dr, 98:2 er) and **14m** (64:36 dr, >99.5:0.5 er) were isolated in 55 % and 72 % yield, respectively. In fact, this is to our knowledge, the first time that simple H_2 instead of Hantzsch pyridine ester is employed for stereoselective hydrogenations of enals [72]. The synthesized carbocycles **14** were also efficiently converted to diols **15** and alcohol **16a** in high yields using $NaBH_4$ and $NaCNBH_3$, respectively. This catalytic asymmetric relay transformation was also highly enantioselective in the assembly of polysubstituted spirocyclic oxindoles **17** (99.5:0.5->99.5:0.5 er) and **18** (Scheme 5b). It is important to note that the synergistic action of the heterogeneous metal/chiral amine co-catalysis significantly accelerated the 1,4-regiospecific

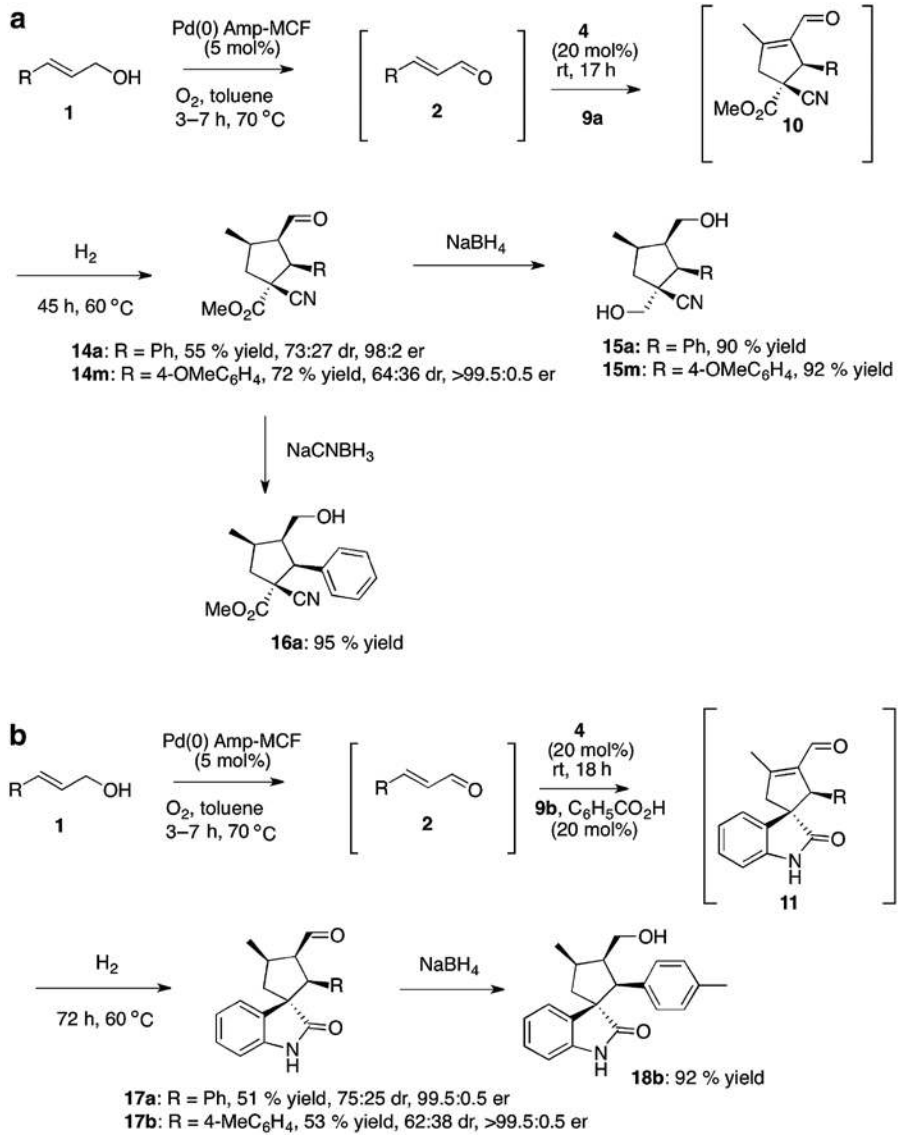


Scheme 3: Examples of ARC at level 2. [a]20 mol% benzoic acid was added. [b]Air, *p*-xylene. [c]Pd(0)-AmP-CPG (5 mol%) was used as the catalyst. [d]$Pd(0)(PPh_3)_4$ was used as the catalyst.



Scheme 4: Results from the catalytic oxidation/Michael/carbocyclization/aziridination relay. (a) Azardination with *ent*-**4**. (b) Azardination with **4**.

hydrogenations of **10**. In fact, the hydrogenation of **10m** using only Pd(0)-AmP-MCF as the catalyst provided only trace amounts of **15m** after 72 h. However, Pd(0)-AmP-MCF (2 mol%) was able to catalyse the hydrogenation of simple cinnamic aldehyde **2a** in full conversion to 3-phenylpropionaldehyde **2a** and 3-phenylpropanol in a 76:24 ratio after 7 h in toluene at room temperature. Performing this reaction under the exact same condition but with the addition of amine **4** (20 mol%) gave 3-phenylpropionaldehyde **2a** and 3-phenylpropanol in



Scheme 5: Results from the catalytic oxidation/Michael/carbocyclization/hydrogenation relay. (a) Synthesis of carbocycles **14–16**. (b) Sythesis of spirocyclic oxindoles **17** and **18**.

a 90:10 ratio after 7 h. In addition, using the same metal/chiral amine co-catalyst system for the hydrogenation of (*E*)-3-phenylbut-2-enal gave 3-phenylbutanal, 3-phenylbutanol and (*E*)-3-phenylbut-2-en-1-ol in 85:10:5 ratios after 3h. In addition, the chiral products from this reaction were nearly racemic [L. Deiana, unpublished results]. The *vide supra* experiments revealed that the reactivity of both the Pd(0)-AmP-MCF particles and the Pd(0)-AmP-MCF/chiral amine catalyst system were very substrate dependent. In particular, the presence of chiral amine **4** was very important to succeed in the 1,4-selective hydrogenation of **10m**. To account for the stereochemical outcome of the final step of the above "level 3" relay sequences we propose transition states (TS) **I**, **II**, **III** and **IV** which are generated by the condensation of carbocycles **10** with amine **4** and *ent*-**4**, respectively (Fig. 1). In all TS, the R-group of the carbocycle effectively shields the *Re*-face of the iminium intermediates and *Si*-face of the enamine intermediates, respectively. The conjugate addition can proceed both via TS **I** and TS **II**. However, the *Si*-facial nucleophilic attack on the iminium intermediate depicted in TS **I** was only allowed when a small nucleophile (hydride vs. TSONHTS) was employed. This could be due to effective shielding by the bulky chiral group of **4**. In fact, in the catalytic aziridination of **10** where TsONHTs is employed as the reagent, the initial conjugate addition went forward via TS **II** instead of TS **I**. Moreover, if

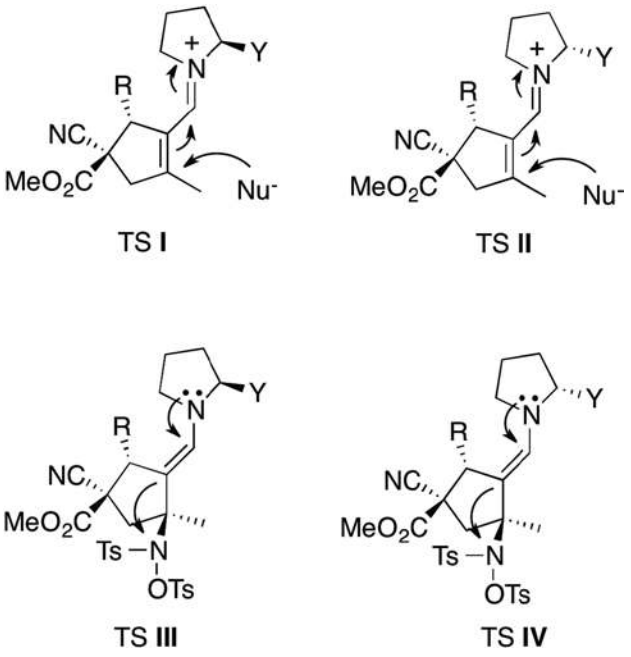


Fig. 1: Transition states (TS) **I–IV**. Nu = Nucleophile, Ts = 4-toluenesulfonyl.

the conjugate addition had followed a pathway via TS **I** the subsequent *Re*-facial intermolecular nucleophilic attack by the enamine intermediate via TS **III** would be significantly disfavored as compared to TS **IV** due to steric shielding by the bulky chiral group of **4**. Thus, *ent*-**4** had to be selected as a catalyst for the aziridination of **10** to occur. The iminium intermediates depicted in TS **I** and TS **II** were confirmed by HRMS analysis [57].

The importance and practical value of the multi-catalytic metal/organo catalyst relay strategy is the recyclability of the heterogeneous catalyst for several cycles. In this context, we haven shown that both the Pd(0)-AmP-MCF and Pd(0)-AmP-CPG catalysts can be recycled after level 2 and level 3. Here both the aerobic oxidation/Michael/carbocyclization (level 2) and aerobic oxidation/Michael/carbocyclization/azirdination (level 3) exhibited excellent recyclability in terms of stereoselectivity and yield. Moreover, no leaching of the metal catalyst was detected [57].

Conclusion

The development of new versatile methodologies leading to novel scaffolds, which can be readily further diversified and provide unprecedented chemical and biological properties is a key aim in organic synthesis. To do this in an eco-friendly and "green" way is of particular interest. Here a sustainable concept for the synthesis of small molecules of varying complexity is presented. Valuable molecules were assembled with high chemo-, regio-, diastereo-, and enantioselectivity in one-pot manipulations from simple alcohols using combined heterogeneous metal/organocatalytic multiple relay catalysis and non-toxic oxidants. Thus, eco-friendly synthesis was accomplished without several purification steps and includes important aspects such as reduction of waste and solvents, the use of hydrogen gas for 1,4-selective hydrogenations, recyclability of the heterogeneous transition metal catalyst and employment of molecular oxygen/air as oxidants. It is important that the interplay between homogeneous and heterogeneous catalyst systems as demonstrated here cannot only be employed as a direct entry to today's knowledge in aminocatalysis but also allow for the creation of novel reactions.

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