Synthetic Methods

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Combined Heterogeneous Metal/Chiral Amine: Multiple Relay Catalysis for Versatile Eco-Friendly Synthesis**

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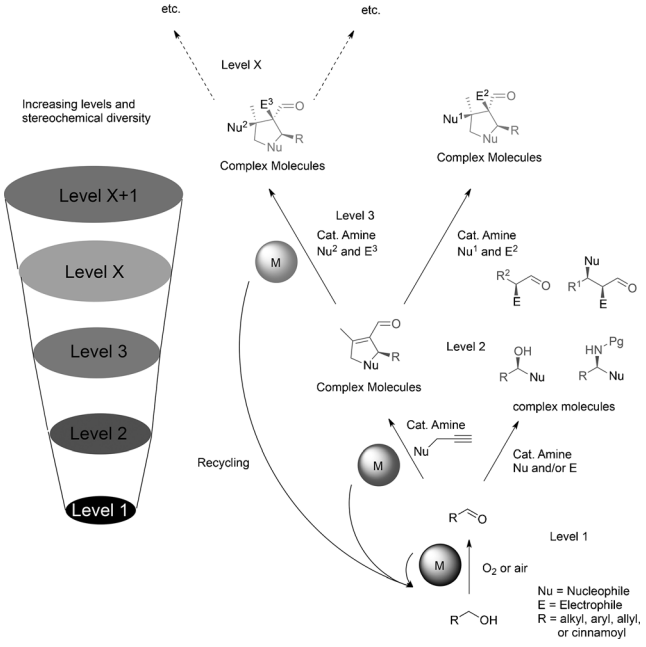
Abstract: *Herein is described a versatile and broad synergistic strategy for expansion of chemical space and the synthesis of valuable molecules (e.g. carbocycles and heterocycles), with up to three quaternary stereocenters, in a highly enantioselective fashion from simple alcohols (31 examples, 95:5 to >99.5:0.5 e.r.) using integrated heterogeneous metal/chiral amine multiple relay catalysis and air/O_2 as the terminal oxidant. A novel highly 1,4-selective heterogeneous metal/amine co-catalyzed hydrogenation of enals was also added to the relay catalysis sequences.*

In practice, organic synthesis operates through stepwise processes where isolation and purification of key intermediates are often required for success in further transformations.[1] This process is in contrast to that of nature, where well-organized multienzymatic systems within cells accomplish efficient and selective one-pot tandem catalyzed transformations of simple precursors into complex molecules.[2] While each discipline of catalysis (i.e., metal catalysis, metal-free catalysis, and biocatalysis) has its own advantages, limitations, and range of applications, the combination of catalytic paradigms to better match biosynthesis are often limited by compatibility problems such as cross-reactivity or mutual inactivation.[3,4] If it were possible to compartmentalize the catalytic species, such as performing catalysis in sequential steps or by site-isolation through immobilization, heterogeneous, or biphasic reaction conditions, then such adversities could be circumvented.[5] The development of increasingly tolerant and robust catalytic systems would bring practical laboratory chemistry closer to the platonic ideal of nature by mediating several transformations in a single reaction event under green chemistry parameters.[3c,6]

In recent years, the development of asymmetric relay catalysis (ARC), which combines homogeneous metal and organic catalysts,[4,7] has attracted considerable attention as a means to new transformations which cannot be achieved using the catalysts individually. An important expansion to this multicatalysis approach would be the inclusion of heterogeneous catalysis since it would allow reactivity not possible using homogeneous organometallic catalysts (e.g. both oxidation and reduction cascade reactions), as well as simple separation and recycling of the expensive and non-environmentally friendly transition metals.[5b,c,8] Thus, we reasoned that merging the powerful paradigms of heterogeneous metal catalysis with organocatalysis and applying it in ARC transformations would produce a carefully designed chiral molecule of particular stereochemistry after a single purification in an operationally simple, efficient, and green manner (Scheme 1). Here the asymmetric construction of quaternary stereocenters is a challenging task in organic



Scheme 1. Combined heterogeneous-transition-metal/chiral amine relay catalysis.

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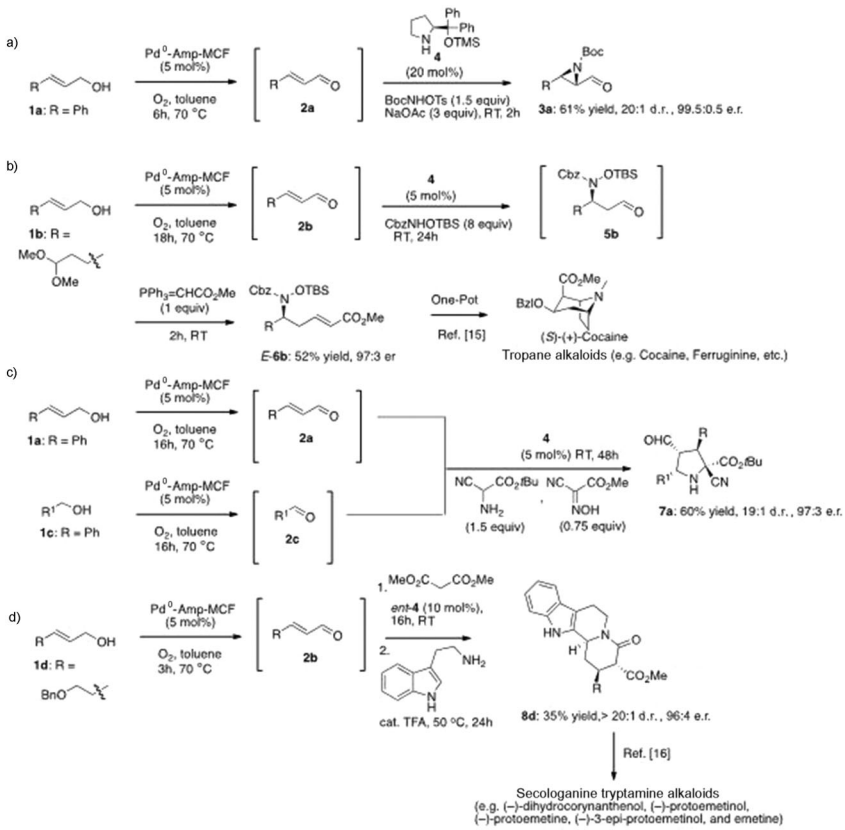
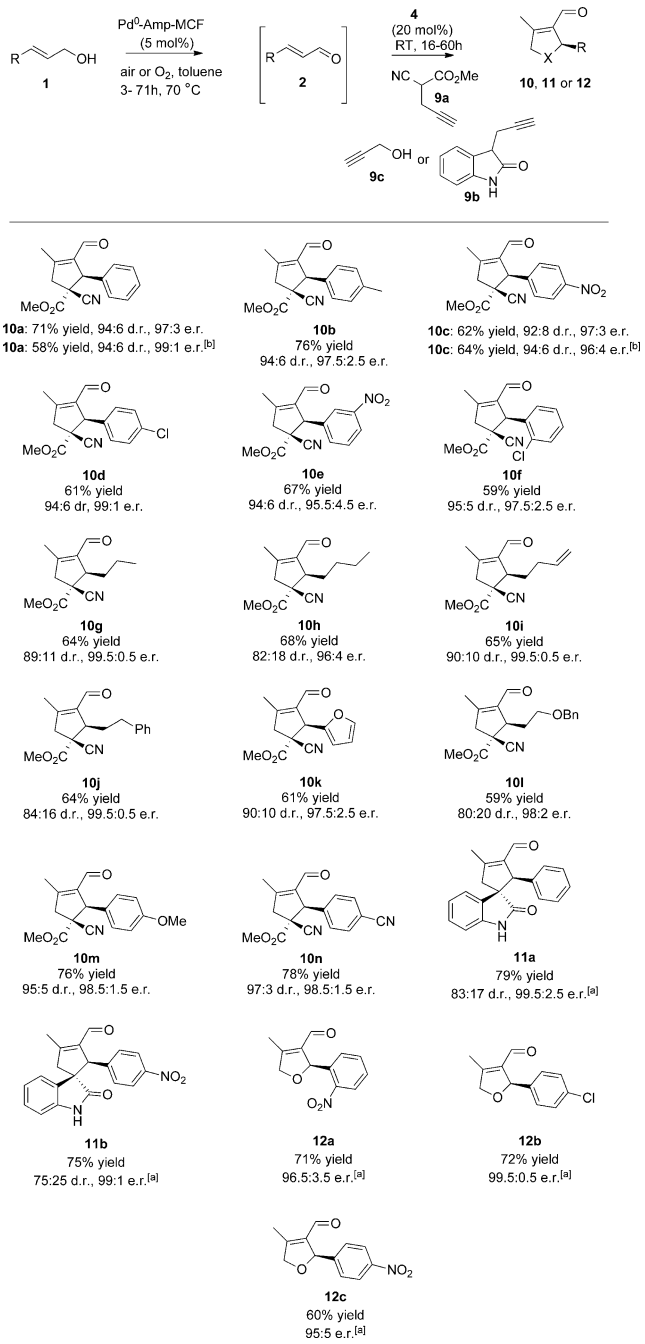
synthesis.[9] The foundation of this strategy lies in the ability of a heterogeneous metal catalyst to take part in multiple cascade sequences co-directed by tandem interactions with small chiral amine catalysts and substrate additives.

Palladium is arguably one of the most powerful and versatile transition-metal catalysts which can be immobilized on various heterogeneous supports and be used for a variety of organic transformations.[10] We recently disclosed asymmetric carbocyclizations implementing a heterogeneous palladium catalyst with a simple chiral amine co-catalyst.[11] The success in this endeavor prompted us to design the proposed multicatalysis relay strategy using a palladium nanocatalyst, where the initial transformation would be the selective aerobic oxidation of alcohols to aldehydes (Scheme 1; level 1). Next, these aldehydes could be further transformed by an organic catalyst into a plethora of molecules, thus unleashing the full potential of aminocatalytic transformations (Scheme 1; level 2).[12] However, such control of the reaction outcome would require strict stipulations. Relay transformations are only possible if the palladium nanocatalyst does not impede or get inhibited prior to or during the subsequent reaction. Furthermore, if the heterogeneous metal catalyst was used in a subsequent synergistic step with the metal-free catalyst, the relay sequence would be perpetuated (level 2). The product from this approach could take part in further relay catalysis sequences as described, thus increasing the complexity and versatility of the strategy (Scheme 1; level 3). Thus, as the catalytic relay sequence continues, a higher level would be reached and importantly the heterogeneous metal catalyst could be recycled after the target molecule is synthesized. Herein we demonstrate a versatile strategy for the synthesis of valuable molecules (up to three quaternary stereocenters) through expansion of chemical space in a highly selective fashion (up to > 99.5:0.5 e.r., 1,4-specific hydrogenation) from simple alcohols using a combination of heterogeneous transition-metal and chiral amine catalysts (Scheme 1).

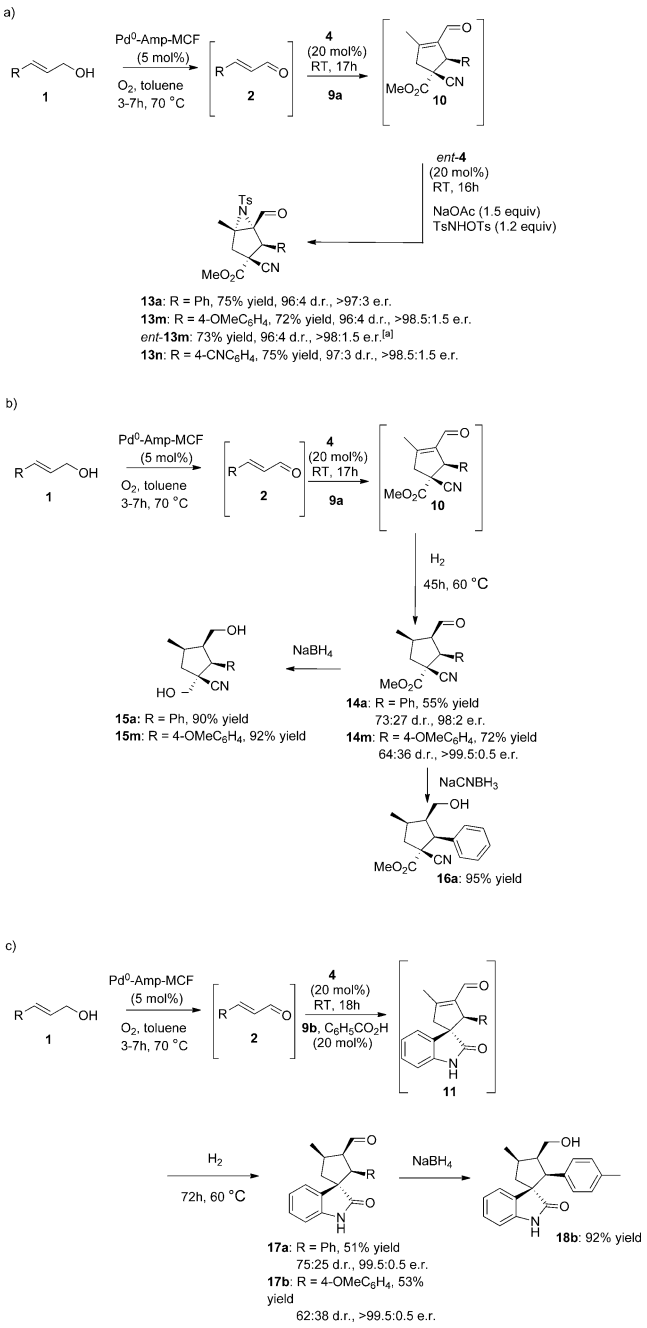


Scheme 2. Examples of co-catalytic relay catalysis at level 2. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

We began our investigations by designing ARC for the level 2 as disclosed in Scheme 1, since it in principle should be possible to apply and implement it for a broad range of aminocatalytic transformations. Thus, several new ARC reactions were developed after extensive efforts using the Pd^0-AmP-MCF-catalyzed aerobic oxidation[10e] of alcohols (**1**) combined with one-pot cascade transformations using the chiral amine **4**[13] as a catalyst (Scheme 2). For example, the aziridine **3a**[14] and δ-amino olefin (*E*)-**6b**,[15] which is rapidly converted into (*S*)-cocaine in one-pot, were assembled in an asymmetric fashion in high overall yields and e.r. values (Scheme 2a,b). The application of parallel aerobic oxidations in sequence with asymmetric multicomponent transformations was also investigated. Thus, the chiral pyrrolidine **7a** (19:1 d.r. and 97:3 e.r.),[16] which has a quaternary α-stereocenter, was synthesized from **1a** by an aerobic oxidation/one-pot three-component cycloaddition catalytic relay using a three-catalyst system (Scheme 2c). The one-pot three-component ARC synthesis of the advanced key intermediate **8d**,[17] which is employed in the total synthesis of several secologanine tryptamine alkaloids, was also successful (Scheme 2d). The above results demonstrate that heterogeneous-palladium-catalyzed aerobic oxidation of the alcohols **1** can be performed in tandem with a large variety of aminocatalytic reactions with carbonyl compounds in one pot without inhibiting the catalytic actions of the amine catalysts. Next, a catalytic enantioselective aerobic oxidation/Michael/carbocyclization relay sequence was examined using air/O_2 as the terminal oxidants (Scheme 1; level 2). This cascade transformation starts with the aerobic oxidation of the allylic alcohol **1** through Pd^0-AmP-MCF catalysis and is followed by the Pd/**4**-co-catalyzed dynamic carbocyclization transformation between the in situ generated enal **2** and either the propargylic cyanoacetate **9a**, propargyl isoindolinone **9b**, or propargyl alcohol **9c** (Scheme 3). The multicatalytic ARC sequences were highly enantioselective, thus providing the corresponding cyclopentenes **10**[18] and spirocyclic oxindoles **11**,[19] each bearing a quaternary stereocenter, as well as the chiral dihydrofurans **12**[20] in high yields and e.r. values



Scheme 3. Co-catalytic enantioselective aerobic oxidation/Michael/carbocyclization relay sequence (level 2). [a] Benzoic acid (20 mol%) was added. [b] Air, *p*-xylene.



Scheme 4. Examples of combined transition-metal/chiral amine relay catalysis (level 3).

(95.5:4.5–99.5:0.5 e.r.). The transformation also exhibited a broad scope in that the allylic alcohols **1** with both electron-rich, electron-deficient, aliphatic, and heteroaromatic substituents were tolerated as starting materials. In comparison, the same relay sequence using homogeneous $[Pd(PPh_3)_4]$ as the co-catalyst is narrower in substrate scope and less efficient.[21]

After probing level 2 of the combined heterogeneous metal/chiral amine ARC concept (Scheme 1), we embarked on the possibility of reaching a higher degree of molecular complexity and construction of vicinal quaternary sterocenters by extending the relay protocol to level 3. A novel aerobic oxidation/Michael/carbocyclization/azirdination catalytic relay sequence was developed (Scheme 4a). Notably, we found that to obtain the desired polysubstituted chiral azirdines **13** (up to 97:3 d.r. and > 98.5:1.5 e.r.), bearing three quaternary stereocenters, *ent*-**4** had to be added as a co-catalyst. If only the chiral amine **4** was used as the co-catalyst, the ARC sequence stopped exclusively at the formation of the cyclopentene **10a**. Thus, in the last step of this ARC transformation **4** was racemic, however, only *ent*-**4** was catalytically active.

An interesting aspect of utilizing a versatile heterogeneous nanocatalyst based on palladium is that it can be used both for aerobic oxidation and hydrogenation reactions. In this context, we envisioned an aerobic oxidation/Michael/carbocyclization/reduction cascade using molecular oxygen as the green oxidant for the first step, and molecular hydrogen as the reducing agent for the last step of the catalytic relay sequence (Scheme 4b). Notably, this would be the first example with simple H_2 instead of the Hantzsch pyridine ester for use in amine-catalyzed stereoselective hydrogenations of enals.[22] The development of this one-pot ARC transformation was successful and the hydrogenation was 1,4-regiospecific and highly enantioselective, thus exclusively the providing polysubstituted cyclopentanes **14**, which contain a quaternary all-carbon stereocenter, from enals **1** in good yields and with up to greater than 99.5:0.5 e.r. Subsequent reduction of **14** with $NaBH_4$ and $NaCNBH_3$ provided the cyclopentanes **15** and **16a**, respectively. The catalytic cascade relay sequence was also successful for the synthesis of the spirocyclic oxoindoles **17** (up to $>$99.5:0.5 e.r.), having a quaternary stereocenter, and subsequent reduction gave the corresponding alcohol **18b** in high yields (92% yield, Scheme 4c). Notably, the synergistic heterogeneous metal/chiral amine co-catalysis both accelerated the hydrogenation of the enal with hydrogen gas, as well as slightly improved the e.r. values of **14** (up to $>$99.5:0.5) and **17** (up to $>$99.5:0.5) as compared to their intermediates **10** and **11**, respectively. In fact, the hydrogenation of **10m** without the chiral amine **4** present gave trace amounts of the product **15m** after 72 h. Crucial to the practical value of this multicatalytic sequence is the ability to reuse the heterogeneous catalyst over multiple cycles, in order to justify its use over homogeneous counterparts. Thus, we investigated the possibility of recycling the palladium nanocatalyst after level 2 and level 3 (see the Supporting Information). Both relay sequences displayed excellent recyclability in terms of yield and stereoselectivity. It is noteworthy that no leaching of the metal catalyst was observed.

In summary, we have developed a unique concept for the synthesis of small organic molecules of varying complexity, and it is based on combined heterogeneous transition-metal/chiral amine relay catalysis. Starting from simple alcohols, valuable molecules are assembled with high chemo-, regio-, diastereo-, and enantioselectivity by catalytic multiple relay sequences without the need for toxic oxidants and numerous purification steps. Thus, the eco-friendly concept presented includes advantages such as the significant reduction of solvents needed for chromatography, use of molecular oxygen/air as the oxidant, hydrogen gas for 1,4-selective hydrogenations, and recyclability of the heterogeneous transition-metal catalyst. Notably, the disclosed model is not only possible to apply as a direct entry to today's know-how in chiral amine catalysis or combined homogeneous transition-metal/amine catalysis with carbonyl compounds, but as demonstrated here, allows the creation of novel transformations.

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