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Cascade Reactions

Merging Metal and N-Heterocyclic Carbene Catalysis: On the Way to Discovering Enantioselective Organic Transformations**

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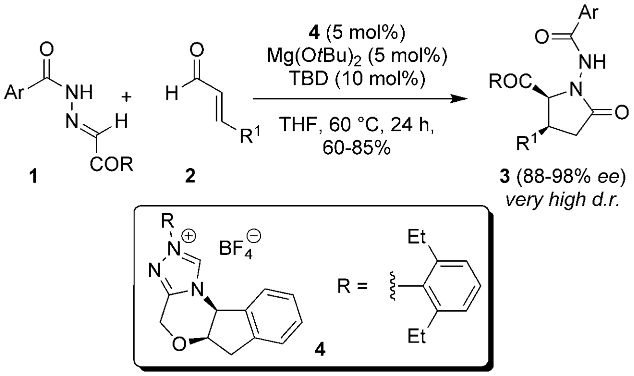
cascade reactions · cooperative catalysis · enantioselectivity · metals · N-heterocyclic carbenes

The first stable N-heterocyclic carbene (NHC) was isolated by Arduengo et al. in 1991.[1] Soon after, NHCs aroused considerable interest among the synthesis community. By virtue of their strong σ-donating ability, NHCs have found remarkable uses as reagents,[2] ligands,[3] and catalysts[4] in organic synthesis. Nowadays, it is relatively easy to develop enantioselective transformations mediated by NHCs owing to the ready availabity of stable, chiral carbenes or their precursors. However, until recently very little was known[5] about the compatibility of a metal (Lewis acid) and a carbene (Lewis base) when used together as catalysts. This lack in knowledge could have arisen from the misconception, which is partly true, that carbenes (Lewis base) act as ligands for metals (Lewis acid), and therefore inhibit the individual reactivity of each component.

Recent research revealed that just such a cooperation is possible and offers unique reactivity that is difficult to achieve with either of the catalysts individually. This cooperative catalysis is challenging because practically, it is difficult to discover the right metal/NHC combination. Unlike biological processes in which nature takes advantage of enzyme architecture to facilitate a reaction cascade, it is difficult to conduct such reactions in a flask. The important feature of this type of cooperative catalysis lies in the fact that the reaction can be made enantioselective by using a combination of an achiral metal complex and a chiral carbene or vice versa.

Scheidt and co-workers reported, for the first time, a cooperative catalytic system consisting of $Mg(OtBu)_2$ and the chiral NHC **4** for the stereoselective and enantioselective synthesis of optically pure γ-lactams **3** from N-acyl hydrazones **1** and α,β-unsaturated aldehydes **2** (Scheme 1).[6] The key to the success is the reversible magnesium–NHC interaction. The proposed mechanism is given in Scheme 2. First, the NHC precatalyst **4** is deprotonated by the base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and the resultant NHC **4a** adds to the α,β-unsaturated aldehydes **2** (Scheme 2; cycle B). The deprotonation of the aldehyde proton generates the homoenolate intermediate **7**,[7] wherein the electron density of the heterocyclic ring can be delocalized onto the β-carbon atom through the diene portion of the molecule. This nucleophilic species **7** then undergoes addition to the hydrazone, which is activated by chelation to magnesium(II) (cf. intermediate **5**). Once the key carbon–carbon bond is formed, the NHC catalytic cycle is completed by the intramolecular acylation of the magnesium-bonded nitrogen atom with concomitant ring closure to give **3**. Finally, the magnesium(II) catalyst is regenerated by dissociation from the γ-lactam **3** to restart in catalytic cycle A (Scheme 2).



Scheme 1. Cooperative catalysis between $Mg(OtBu)_2$ and the NHC **4**.

Pioneering work from the group of Scheidt revealed another cooperative system that successfully combines $Ti(OiPr)_4$ catalysis and carbene catalysis to provide direct access to substituted cyclopentenes **9** from the α,β-unsaturated aldehyde **2** and α,β-unsaturated ketone **8**, with high enantio- and diastereoselectivity (Scheme 3).[8] Mechanistically, the coordination of aldehyde **2** to the titanium Lewis acid promotes the formation of the extended Breslow intermediate **10** (Scheme 4). The subsequent coordination of the chalcone to this carbene/aldehyde/titanium(IV) intermediate activates the enone towards conjugate addition as well as situates the homoenolate in close proximity to the β-carbon atom of enone **11**. The conjugate addition involves the

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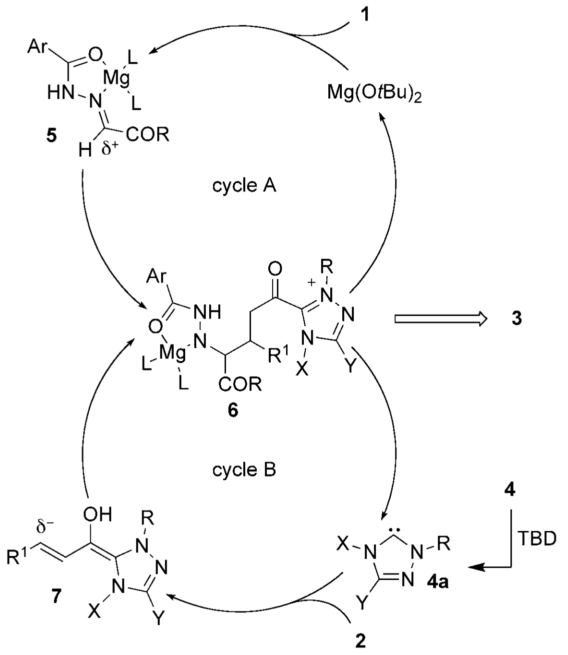
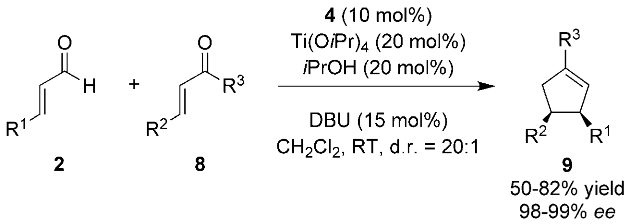
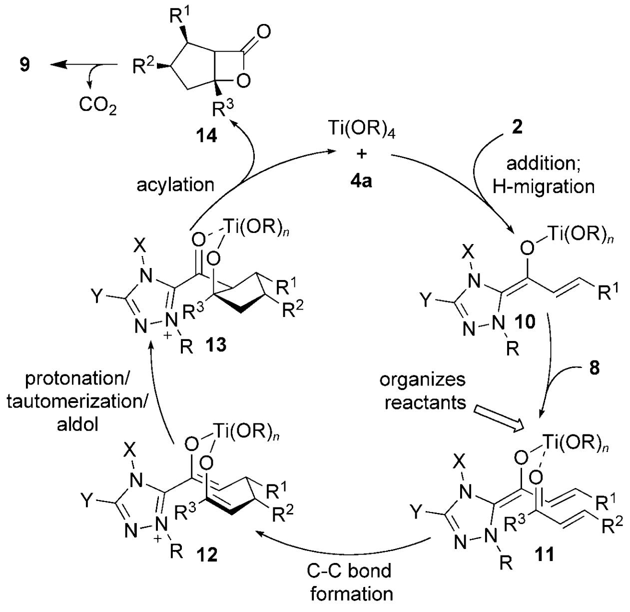


Scheme 2. Mechanism for the cooperative catalysis between Mg(O*t*Bu)$_2$ and NHC **4**.



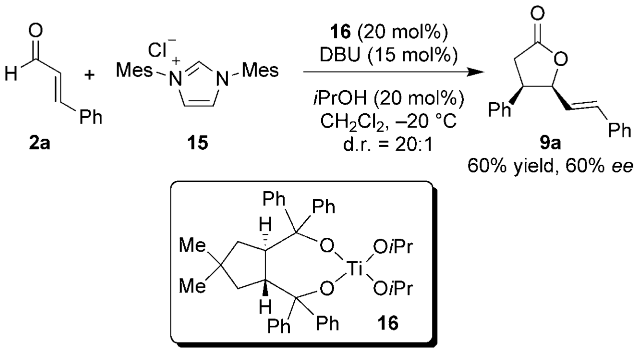
Scheme 3. Cooperative catalysis between Ti(O*i*Pr)$_4$ and the NHC **4**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 4. Mechanism for cooperative catalysis between the metal and the NHC **4**.

chalcone reacting in the s-*cis* conformation to generate the bis(enolate) **12**. The protonation and tautomerization of this chalcone carbonyl titanium enolate and the resulting intramolecular aldol reaction affords the intermediate **13**. Finally an acylation and decarboxylation cascade (**13**→**9**) occurs to give cyclopentenes. The proposed role of 2-propanol was to accelerate the acylation step from **12** to regenerate the carbene catalyst and Ti(O*i*Pr)$_4$ by facilitating the dissociation of the tertiary alkoxide.

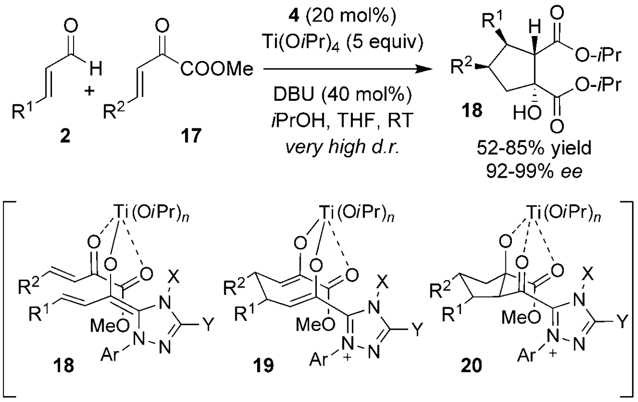
The excellent results obtained with this metal/NHC cooperativity prompted the authors to evaluate the possibility of combining an achiral Lewis acid and a chiral carbene as a catalyst. Indeed, the reaction of **2a** in the presence of Ti/(*R*,*R*)-taddol (**16**) and IMes (**15**) as the catalyst proceeded to give the *cis*-γ-butyrolactone **9a** in 60 % yield with 60 % *ee* and high diastereoselectivity (Scheme 5). The observed enantiomeric excess in the product clearly indicated that the Ti^{IV} catalysis is involved in the key bond-forming event. This result is promising because the use of two catalysts allows either one or both of the components to be optically active, thereby providing new standards in these reaction cascades.



Scheme 5. Cooperative catalysis between Ti/(*R*,*R*)-taddol and the achiral NHC **15**.

Very recently, Scheidt and co-workers extended[9] the use of the Ti(O*i*Pr)$_4$/NHC (**4**) catalyst system for the diastereo- and enantioselective annulation of enals **2** and β,γ-unsaturated α-ketoesters **17** for the synthesis of densely functionalized cyclopentanes **18** (Scheme 6). They employed 5 equivalents of Ti(O*i*Pr)$_4$, but the reason for the use of excess catalyst is unclear. Mechanistically, the reactants **2** and **17** deliver **18** in the presence of **4**. The intramolecular conjugate addition to give **19** and subsequent protonation, tautomerization, and intramolecular aldol reaction afforded the intermediate **20**. Subsequent acylation and transesterification gives cyclopentanes **18**. In the present case the use of achiral NHCs and chiral Ti^{IV} complexes did not provide the desired products.

In the two-catalyst system the NHC and metal operate concurrently to give products that are not accessible by using one of the catalysts; this clearly indicates the importance of such processes in synthetic organic chemistry. However, at present the successful examples are limited and reactions are specific. Additional challenges for this chemistry could include the development of novel compatible catalysts. Since



Scheme 6. Annulation of enals **2** and β,γ-unsaturated α-ketoesters **17** catalyzed by Ti(O*i*Pr)$_4$/NHC (**4**).

there are several metal salts available and several NHCs can be structurally tuned, the combinations are unlimited, and therefore a number of new reactivity patterns can be expected for this type of catalysis in the near future. The fact that NHCs are compatible with late-transition metals such as palladium[5] and silver[10] may provide an impetus to this area of research.

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