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Cooperative Catalysis by Carbenes and Lewis Acids in a Highly Stereoselective Route to γ-Lactams

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Abstract

Enzymes are a continuing source of inspiration for the design of new chemical reactions that proceed with efficiency, high selectivity and minimal waste. In many biochemical processes, different catalytic species, such as Lewis acids and bases, are involved in precisely orchestrated interactions to activate reactants simultaneously or sequentially. Employing this type of *cooperative catalysis*, in which two or more catalytic cycles operate concurrently to achieve one overall transformation, has great potential to enhance known reactivity and drive the development of new chemical reactions with high value. In this disclosure, a cooperative *N*-heterocyclic carbene/Lewis acid catalytic system promotes the addition of homoenolate equivalents to hydrazones generating highly substituted γ-lactams in moderate to good yields and high levels of diastereo- and enantioselectivity.

Biological systems have evolved to activate substrates using acids and bases simultaneously within an active site. Proteases achieve astounding efficiency in the hydrolysis of robust amide bonds by utilizing a serine or cysteine (Lewis base), an aspartic acid residue (Brønsted acid) and a histidine residue (Brønsted base) in concert. This catalytic triad is essential for life processes and the precise placement of these catalytic functional groups precludes non-productive interactions. In general, Nature utilizes enzyme architecture to facilitate a cooperative reaction manifold since many catalytic sites contain functional groups and/or metals that would be incompatible in simple solution-based chemistry. For example, the reactive thiol of an acyl transferase would bind to the active iron center in a cytochrome if either one was removed from their protein framework. It has been a significant challenge to capitalize on this powerful cooperative concept with abiotic systems. In systems utilizing *cooperative catalysis*, the combination of Lewis acid *and* Lewis base activation can achieve greater selectivity and more efficient reactivity than either mode individually while simultaneously avoiding any substantial self-inhibition.1–6 However, homogenous catalytic reactions promote random collisions of all species in solution, facilitating simple acid-base chemistry or the generation of stable Lewis acid•Lewis base

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Author contibutions: K.A.S. conceived the idea and wrote the manuscript. D. E. A. R., B. C.-D. and D.H. performed the experiments. All the authors analysed the data. K.A.S., D. E. A. R., B. C.-D contributed to discussions and edited the manuscript.

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complexes which will compete with a desired catalytic reaction. Inspired by the thiamine pyrophosphate cofactor,7,8 *N*-heterocyclic carbenes (NHC) have emerged as unique and efficient Lewis base catalysts9–11 for a host of new reactions over the last decade, including the generation of acyl anion equivalents,12–17 homoenolate equivalents,18–23 enolates, 24,25 and acylvinyl anion equivalents.26 However, NHCs have not been utilized cooperatively with Lewis acids to generate new carbon-carbon bonds, presumably since these species *act as exceptional ligands for late transition metals* (Figure 1).27–33 This issue has only been overcome once previously in the literature in a reaction utilizing NHC's and palladium in separate catalytic cycles.34

We disclose herein a cooperative and catalytic *N*-heterocyclic carbene/Lewis acid system, and demonstrate its utility with the highly enantioselective addition of homoenolate equivalents to Lewis acid-activated *N*-benzoyl hydrazones. In this novel strategy, the *N*-heterocyclic carbene combines transiently with an aldehyde to generate an unusual nucleophile and raise the energy of the highest occupied molecular orbital (HOMO). Simultaneously, an optimal Lewis acid catalyst activates the hydrazone by lowering the energy of the lowest unoccupied molecular orbital (LUMO) for an overall productive reaction.

We have been investigating new classes of electrophiles with homoenolate equivalents generated using *N*-heterocyclic carbene catalysis to gain direct access to highly useful γ-amino acid derivatives35,36 or natural products.37 To achieve this goal, an effective class of imine was required which could deliver highly substituted γ-lactams with high levels of enantioselectivity and diastereoselectivity. 23,38 If successful, this formal [3+2] annulation process could, from two simple starting materials and a small organic molecule catalyst, directly produce important five-membered heterocycles with known biological activity and high occurrence in the structures of natural products. *N*-acyl hydrazones are well known substrates for both Lewis acid-activated cycloadditions and nucleophilic allylation reactions. 39 In these processes, the hydrazone substrates presumably undergo activation by chelation to a Lewis acid with the carbonyl oxygen and imine nitrogen atoms to form an activated electrophile in situ. Our studies exploring the formal cycloadditions employing *N*-benzoyl hydrazones and various unsaturated aldehydes were initiated by treating cinnamaldehyde and hydrazone **1a** with a variety of azolium salts and subjecting the mixture to a number of reaction conditions. The catalyst generated from benzimidazolium **4** displayed promising reactivity during the preliminary screening although incomplete conversion of **1a** was observed. After surveying both amine and inorganic bases, the bicyclic guanidine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was found to efficiently promote the formal [3+2] cycloaddition. The basicity of TBD in THF is higher ($TBDH^+$ pK_a = 21.0) than DBU ($DBUH^+$ pK_a =16.8), which has been heavily used as a base in reported carbene-catalyzed reactions.40 With these initial conditions, we examined the impact of chiral triazolium salts on the efficiency and stereoinduction of the process. While the reaction progressed with moderate selectivity utilizing chiral triazolium **5** (72% ee, entry 4), higher levels of absolute stereocontrol could not be obtained by lowering the temperature, changing the base or employing various protic additives (not shown). Additionally, the yield of the reaction

dropped from 90% (entry 3) to 62% (entry 4) due to incomplete consumption of the hydrazone, a situation that could not be remedied with a single catalyst approach.

We hypothesized that the overall process might benefit from increasing the electrophilicity of the hydrazone substrate and thus undertook an investigation combining carbene catalysts with Lewis acidic additives. This strategy to employ nucleophilic carbenes as Lewis base catalysts in the presence of hard, oxophilic Lewis acids is a challenging goal with significant potential. If successful, the ability to modulate the available electron density of the nucleophile and the electrophile *simultaneously in two distinct catalytic cycles offers unique opportunities for new reaction discovery and development* (Figure 1). After an extensive survey of early transition and alkali metal salts, the use of 20 mol % magnesium di-*tert*-butoxide41 improved the reaction significantly both in terms of yield and selectivity (entry 5). Lanthanide trifluoromethanesulfonates (triflates), such as $La(OSO_2CF_3)_3$, completely inhibited homoenolate addition even with an equivalent molar amount of base (e.g. sodium *tert*-butoxide) to preclude the possibility of poisoning by trace acid. Transition metal triflates, such as $Cu(OSO_2CF_3)_2$ and $Zn(OSO_2CF_3)_2$, were not catalysts alone, but the addition of base allowed a very modest progression toward the desired lactam over 24 hours (10–30% conversion of hydrazone **1a**). The addition of titanium(IV) alkoxides resulted in very sluggish reactions with only 40% conversion of hydrazone **1a** after 24 h. Magnesium (II) halides or triflates did not impede the progress of the reaction, but did not improve the results compared to experiments with only NHCs. Magnesium (II) di-*tert*-butoxide emerged as the optimal Lewis acid in terms of enhanced reaction rates, hydrazone conversion and isolated yields. In addition to optimizing the Lewis acid component, a survey of different chiral triazolium salts identified the 2,6-diethyl substituted azolium **7** as the superior catalyst in terms of enantioselectivity both with and without the Lewis acid additive (entries 7–10). The significant and beneficial impact of this cooperative catalysis protocol becomes evident when decreased loadings of magnesium(II) and azolium salts are employed. For example, both azolium and Mg(II) source can be lowered to 5 mol % without affecting the yield of the reaction or the high levels of enantioselectivity (entry 10). Decreasing the NHC loading without the Lewis acid has a deleterious effect on both yield and conversion (entry 9).

The proposed cooperative catalytic cycles are outlined in Figure 2. The azolium pre-catalyst is deprotonated by the base (TBD) and the resultant carbene (**NHC**) adds to the α,β-unsaturated aldehyde. The deprotonation of the aldehyde proton generates the homoenolate equivalent (enediamine intermediate **II**) in which the electron density of the heterocyclic ring can then be translated to β-carbon via the diene portion of the molecule. This nucleophilic species (**II**) then undergoes addition to the hydrazone which is activated by chelation to magnesium(II) (intermediate **I**). (However, no significant change in chemical shift of any of the hydrazone signals was observed by ^{1}H NMR upon the addition of $Mg(O\textit{t}\text{-}Bu)_2$.) Once the key carbon- carbon bond is formed, the NHC-catalytic cycle (cycle 2) is completed by the intramolecular acylation of the magnesium-bonded nitrogen (Mg–N) with concomitant ring closure. Finally, the magnesium (II) catalyst is regenerated by dissociation from the γ-lactam product to restart in the catalytic cycle 1.

Our initial mechanistic investigations of the reactions allow for a cooperative catalysis interpretation. Preliminary kinetic studies were explored to begin elucidating the role of the

$Mg(O\textit{t}\text{-}Bu)_2$. Initial-rate kinetic studies were undertaken at five concentrations of the magnesium salt in triplicate to determine the kinetic order of the magnesium. When the k_{init} values for each experiment were calculated and plotted against the concentration of the magnesium (II) salt utilized, the best fit model of kinetic data reaction indicates an *inverse* first order for $Mg(O\textit{t}\text{-}Bu)_2$ (Figure 2b). This result indicates one of two mechanistic possibilities for the magnesium salt. The first is that the Lewis basic NHC species is participating in reversible binding to the Lewis acidic magnesium and the higher concentration of magnesium salt is simply shifting the equilibrium toward the magnesium-bound azolium species, for which ^1H and ^{13}C NMR spectroscopy as well as X-ray crystal structure experiments to observe and/or isolate this complex have not yet been successful. If this reversible magnesium-NHC interaction is taking place, then it is not likely that the two catalytic species are part of a frustrated Lewis acid-base system.42 However, TBD is also Lewis basic and may undergo reversible binding to the magnesium, thus shifting the equilibrium between the active azolium/protonated TBD and protonated azolium/free-base TBD toward the inactive precatalyst.

With the optimized catalysis conditions identified, a variety of hydrazones with modified *N*-aryl groups were surveyed as potential substrates. Mild to moderate electron withdrawing groups on the aromatic ring were well tolerated (e.g., *para*-halogen). Without 5 mol % Mg(II), less than 50% conversion was observed when hydrazone substrates possessed electron rich aryl substituents (e.g. 4-MeO-C_6H_5). However, in this cooperative catalysis manifold the yields with these substrates now regularly fall between 70 and 80% (**3ca**, **3ha**). When varying the imine portion of the substrate, glyoxylate-derived hydrazones, including an oxazolidinone-containing substrate (**3ba**) reacted efficiently while hydrazones from aryl aldehydes (e.g., benzaldehyde) are still not electrophilic enough to undergo this annulation even with Mg(II) activation. (not shown)

The aldehyde scope was surveyed and a variety of functionalities proved to be well tolerated. Weakly electron withdrawing groups (Br, Cl) also performed well under the reaction conditions (**3ad–g**). Electron-rich substrates were very well accommodated, including the 2-furyl-substituted enal which was problematic in earlier studies without the Lewis acid additive (**3ah**). Finally, an alkyl-substituted enals gave moderate yield and excellent selectivity (**3aj, 3al, 3am**) accommodating gamma-branching and even silyl protecting groups.

The cyclic products from this new reaction can be easily converted into high value pyroglutamic acid derivatives, thereby leveraging the utility of the overall process. For example, exposure of γ-lactam **3aa** to Raney-Nickel and H_2 in methanol promotes N–N bond scission in high yield (92%, Figure 3). This 3-phenyl-pyroglutamic ester (**8**) is a known advanced intermediate for the synthesis of clausenamide, a natural product that promotes a protective effect on the liver against toxins such as carbon tetrachloride and thioacetamide and also up-regulates cytochrome P450 enzymes.37,43 Alternatively, the amide of this unnatural amino ester can be selectively reduced to afford 3-phenyl proline derivatives.44 These compounds are known agonists for the melanocortin-4 receptor (MC4R), a G-protein coupled receptor involved in the regulation of appetite, and are potential treatments for anxiety and depression.35 Various substituted prolines have been

used to impart desirable structural attributes and metabolic stability in peptides and proteins, and the enantioselective synthesis of compounds such as **9** should fuel further studies in this area.45 Finally, these pyrrolidines also possess the necessary characteristics for secondary amine/iminium catalysis and new proline-derived catalysts can be generated using this route.46,47

In summary, a new formal [3+2] reaction combining α,β-unsaturated aldehydes and hydrazones has been discovered using a novel cooperative catalysis concept. The integration of two distinct catalytic cycles involving both Lewis basic *N*-heterocyclic carbenes and Lewis acidic magnesium(II) salts facilitates the rapid and controlled production of γ-lactams in high yields and with exceptional levels of diastereo- and enantioselectivity. Each mode of catalysis, both carbene and Lewis acid, enhances the reactivity of the nucleophilic and electrophilic substrates, respectively. This use of nucleophilic carbene catalysis in cooperation with Lewis acid activation highlights an under explored area of catalysis with significant potential. These initial studies demonstrate the broad potential utility and feasibility of combining Lewis basic carbenes with Lewis acids and should lead to many more powerful and highly efficient bond-forming reactions not currently available using either reagent singly. Cooperative carbene catalysis will continue to grow and facilitate new strategies to access important target molecules for use in chemical biology, catalysis, and medicine.

Methods

Hydrazone **1** (0.273 mmol), catalyst **7** (5 mol%), and $Mg(OtBu)_2$ (5 mol%) were combined in a 2 dram oven dried vial and capped with a Teflon/silicon septum inside of a nitrogen drybox. The vial was removed from the drybox and THF (0.25 M) was added and the vial was heated with moderate stirring in an aluminum heating block to 60 °C for 15–20 minutes. The white suspension turned clear and yellow over the course of the initial heating. Unsaturated aldehyde **2** (1.5 equiv) and then TBD (10 mol %) was immediately added. The reaction was allowed to continue at 60 °C and was monitored by TLC (5% MeOH/$CHCl_3$) Upon completion (24 h), the reaction was diluted with CH_2Cl_2 (15 mL) and washed with a 1:1 mixture of saturated aqueous NH_4Cl and water (10 mL). The aqueous layer was back extracted CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The brown oily residue was purified by flash column chromatography on a Biotage SP-1 chromatography system using a 12–100% ethyl acetate/hexanes gradient to yield the desired product **3**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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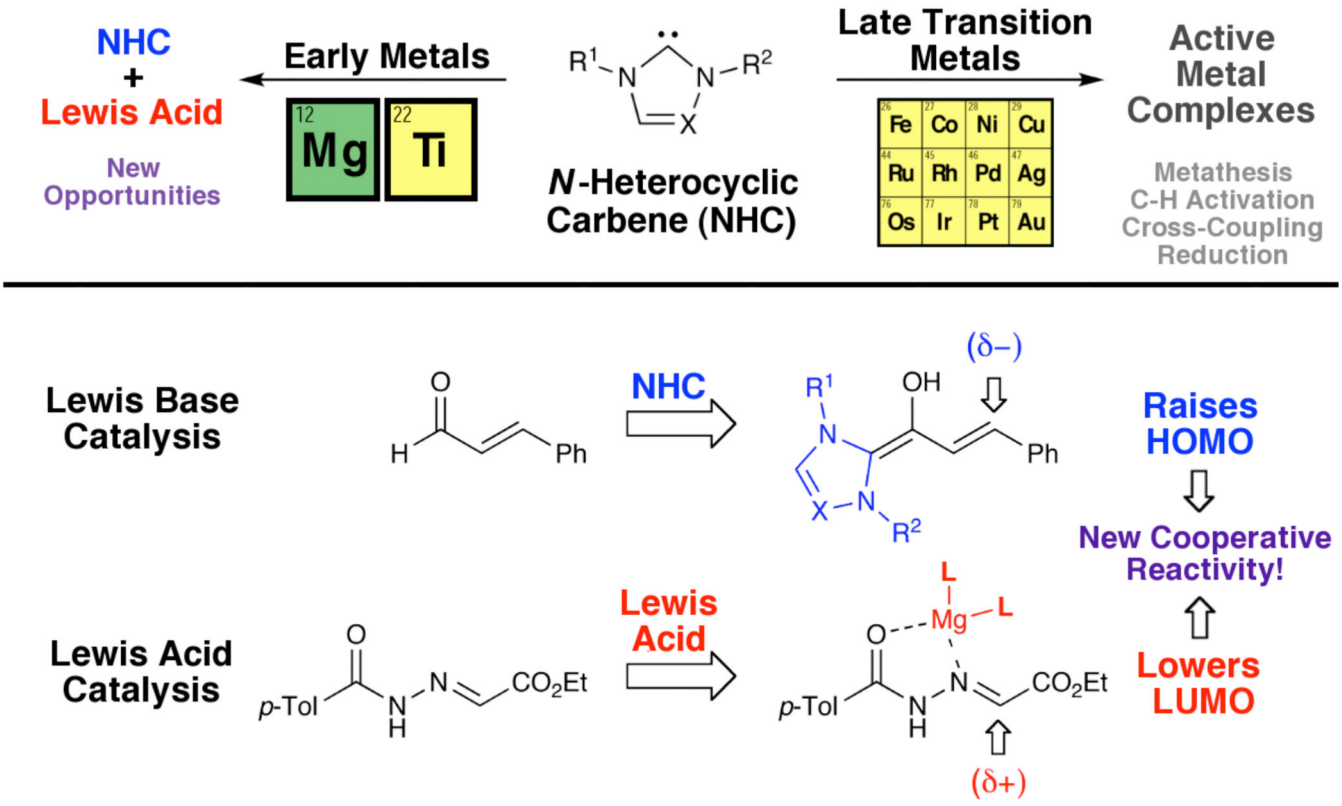


Figure 1.

Opportunities with N-Heterocyclic Carbenes and Metals: It has been well established that NHC's react with enals to furnish a new nucleophilic species and that metal salts can activate chelating electrophiles, such as N-acyl hydrazones. Can both of these processes operate in one flask to access reactivity that is otherwise impossible/inefficient?

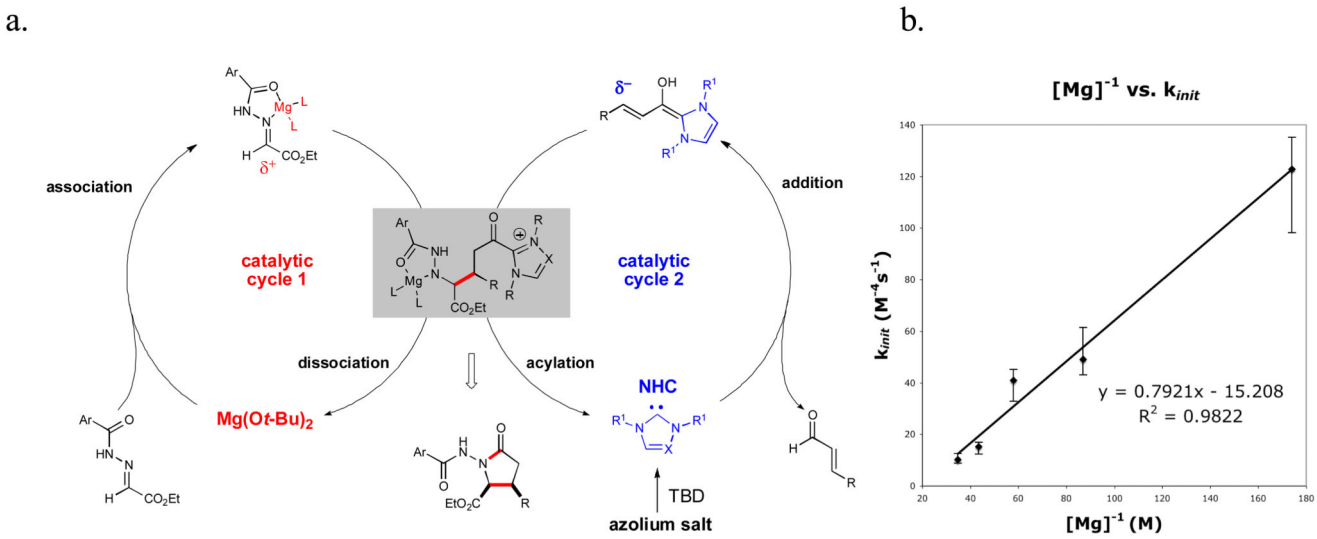


Figure 2.

a. Proposed Cooperative Catalytic Cycles 1 & 2 b. Preliminary Data Concerning the Kinetic Order of Mg(O*t*-Bu)$_2$

a. Proposed catalytic cycles 1 (Mg(O*t*-Bu)$_2$) and 2 (NHC) meeting at a the critical bond-forming step (box) b. Average k_{init} values plotted versus the concentration of Mg(O*t*-Bu)$_2$ to the **negative** first power. The experiments were performed with **1a**, cinnamaldehyde, catalyst **D**, TBD, phenyltrimethylsilane as an internal standard and a range of concentrations of Mg(O*t*-Bu)$_2$ in 1 mL of THF-d8. ^{1}H NMR spectroscopy (400 MHz) was used to monitor the concentration of the product (**2a**). The error bars represent 50% of the minimum and maximum values for k_{init} calculated. See the supporting information for further details.

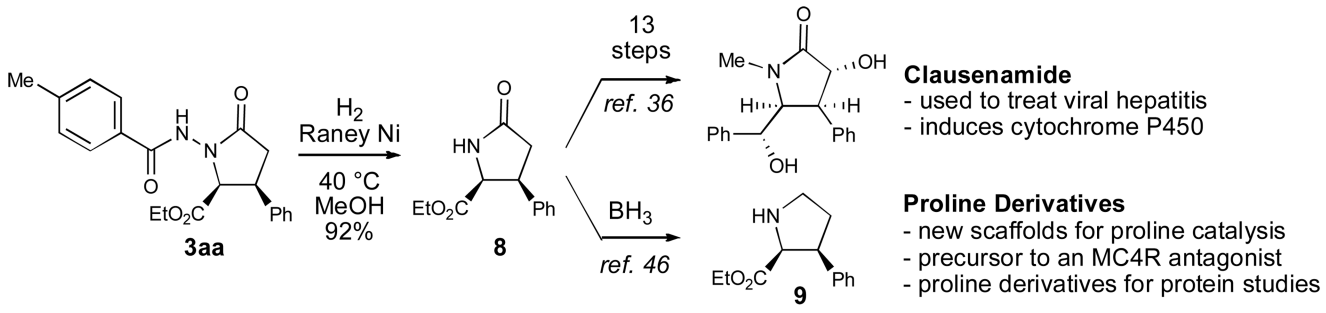
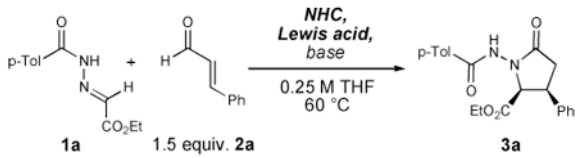


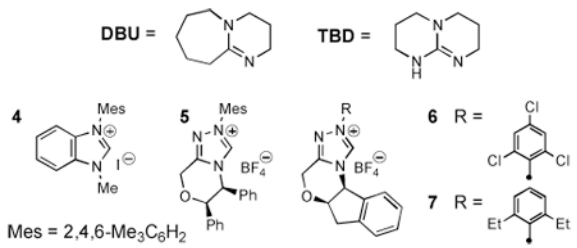
Figure 3.
N–N Bond Cleavage and Further Functionalization

Table 1

Development of Cooperative Carbene Catalysis Reaction



entry	NHC/Lewis acid	base	% yield[a]	dr[b]	% ee[c]
1	20 mol % **4**	1.2 equiv. DBU	58	6:1	—
2	20 mol % **4**	20 mol % TBD	70	12:1	—
3	20 mol % **5**	25 mol % TBD	62	6:1	72
4	20 mol % **5**/Mg(O*t*-Bu)$_2$	25 mol % TBD	78	7:1	86
5	20 mol % **6**/Mg(O*t*-Bu)$_2$	25 mol % TBD	84	7:1	80
6	20 mol % **7**	25 mol % TBD	63	6:1	90
7	20 mol % **7**/Mg(O*t*-Bu)$_2$	25 mol % TBD	79	7:1	97
8	5 mol % **7**	10 mol % TBD	31	6:1	90
9	5 mol % **7**/Mg(O*t*-Bu)$_2$	10 mol % TBD	78	7:1	97



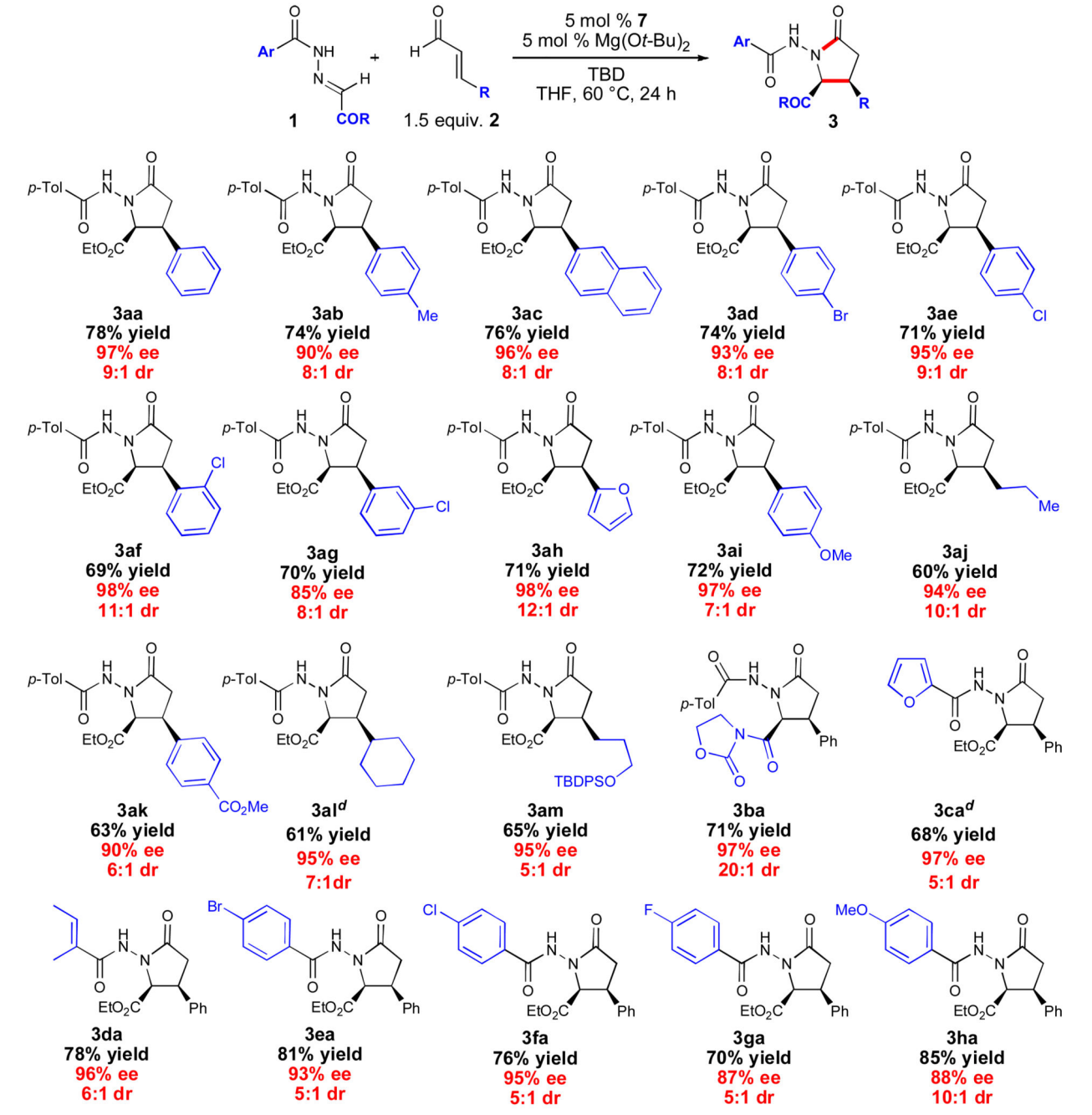
[a] isolated yields.

[b] determined by ^{1}H NMR spectroscopy.

[c] determined by HPLC (chiral stationary phase).

Table 2

Reaction Scope[a,b,c]



[a] isolated yields.

[b] % ee determined by HPLC.

[c] dr determined by ^{1}H NMR spectroscopy.

[d] 10 mol % NHC/Mg)O*t*- Bu)$_2$, 15 mol % TBD