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Redox Economic Synthesis of Trisubstituted Piperidones via Ruthenium Catalyzed Atom-economic Couplings of N-protected 1,5-Aminoalcohols and Michael Acceptors

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Abstract. An efficient atom-economic coupling of 1,5-amino alcohols and Michael acceptors has been developed employing [CpRu(MeCN)$_3$]PF$_6$ as a key catalyst to synthesize α,β-unsaturated ketones with exclusive generation of *E*-geometrical isomers at room temperature without any co-catalyst and additives. A base catalysed 6-*endo-trig* cyclization of the α,β-unsaturated ketone delivers a direct access to tri-substituted piperidones.

Keywords: Atom-economic coupling; Michael acceptor; Tris(acetonitrile)cyclopentadienylruthenium(II) hexafluorophosphate; *E*-geometrical isomer; 6-*endo-trig* cyclization

The remodelling of reactions towards synthetically efficient transformations of simple building blocks into complex molecular targets constitute a fundamental goal. The piperidines resemble one of such important alkaloid cores mentioned for clinical and pre-clinical trials.[1],[2] Thus, catalytic synthetic approaches towards synthesis of these nitrogen heterocycles are highly sought after.

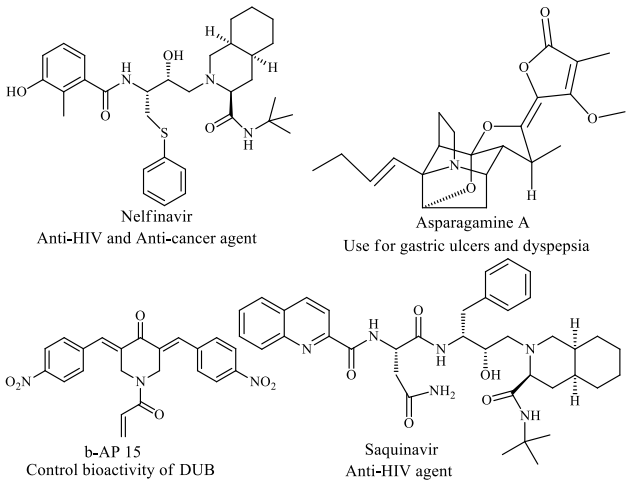
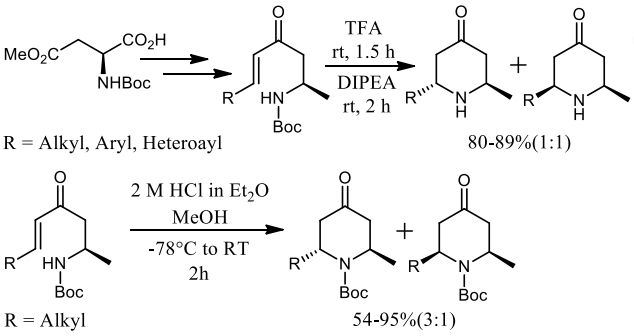


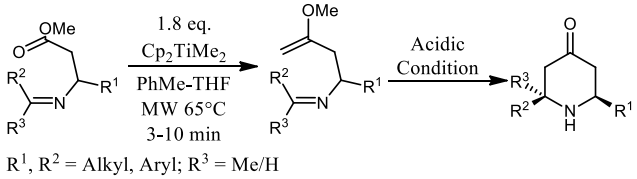
Fig 1. Bioactive Piperidine and Piperidone molecules.

The recent identification of 3,5-bis(phenylmethylene)-1-(N-acyl)-4-piperidones as present in b-AP-15 as prominent cytotoxic agents has further hyped the synthetic attraction.[3],[4],[5],[6] The piperidones serve as among the best available precursors to piperidines. The available literature exemplifies a significant bioactivity associated with the plethora of such aza-heterocycles.[7] Interestingly, ring contraction strategies of piperidines to form pyrrolidines can be an easy way towards the synthesis of these five membered heterocyles as well.[8] Further 2- and/or 6- substituted piperidones are found to unveil more biological activity.[9] Access to 2,6-disubstituted-4-piperidones via an acid and base catalysed cyclization of (E)-enones has been disclosed by the Sutherland group, but the synthesized piperidones always required a vinylic methyl-substitution for the planned 6-*endo-trig* cyclization as depicted in **Scheme 1**.[10a,10b]



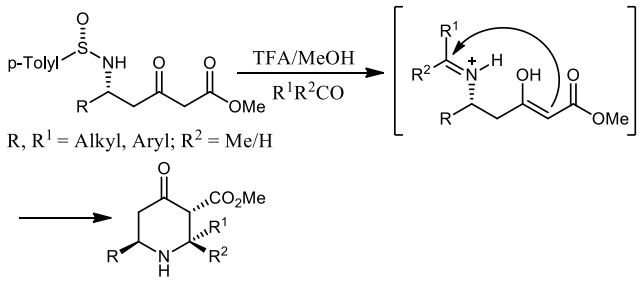
Scheme 1. Acid and base catalyzed piperidone synthesis from amino acid

The Hartley group employed a Petasis olefination for the piperidone synthesis as depicted in **Scheme 2**.[11]



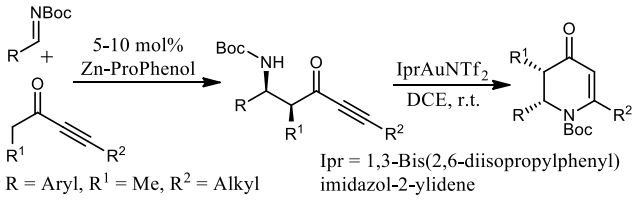
Scheme 2. Acid catalyzed trisubstituted piperidone synthesis via Petasis Methylenation from β-amino acids

Davis disclosed a TFA mediated intramolecular Mannich reaction of S-amino β-keto ester with aldehyde and ketones to deliver poly substituted piperidones as depicted in **Scheme 3**.[12]



Scheme 3. Tetrasubstituted piperidone synthesis employing intramolecular Mannich reaction of δ-amino β-keto esters with aldehydes and ketone

An approach, we developed uses Zn-prophenol catalysed addition of ynones to *N*-Boc imines followed by *6-endo-dig* cyclisation with *in-situ* generated $IprAuNTf_2$ to deliver dihyropiperidin-4-one synthesis as depicted in **Scheme 4**.[13]

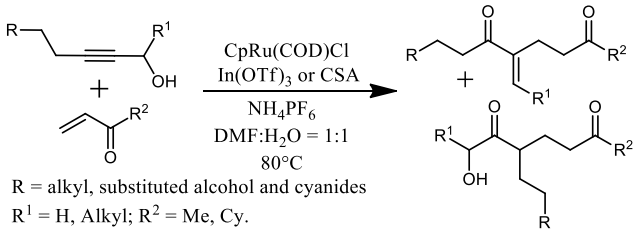


Scheme 4. Gold catalyzed trisubstituted dihydropiperidone-4-one synthesis via addition of alkynyl ketone to imine

Thus, efficient syntheses of substituted piperidones especially emphasizing catalysis represents an immediate key challenge to be addressed. Herein, we report a simple and efficient atom-economic coupling reaction of N-protected-5-aminopent-2-yn-ol with Michael acceptors using $[CpRu(MeCN)_3]PF_6$ as a key step to generate the precursors to substituted 4-piperidones with excellent yields. Further, these may be easily reduced to the corresponding piperidine analogues. A second key step involves a 6-*endo-trig* ring annulation.

The rationale behind electing the ruthenium catalysed coupling arrives from our earlier efforts to add ruthenium complexed allenols with Michael acceptors like methyl vinyl ketones in the presence of the first generation ruthenium catalyst CpRu(COD)Cl.[14] The reactions delivered modest yields along with unwanted generation of branched alcohol as a by-product. The presence of a co-catalyst and elevated temperatures were also required for the reaction as shown in **Scheme 5**.

Previous Work

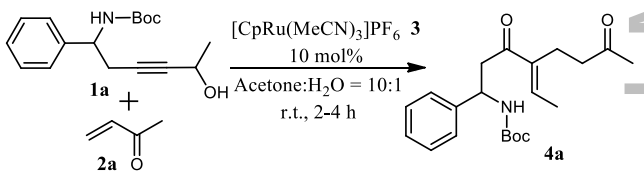


Scheme 5. CpRu(COD)Cl catalyzed coupling reaction of propargyl alcohol and Michael acceptor

Thus, we sought an improved replacement of the earlier protocol with the concomitant generation of substituted piperidones in the process. The study began with the reactions of Boc-amino alcohol (**1**) and *α,β*-unsaturated ketones (**2**) in presence of 10 mol% $[CpRu(MeCN)_3]PF_6$ (**3**) at room temperature (**Scheme 6**) . The *tris*-acetonitrile ruthenium catalyst **(3)** was prepared as per our protocol.[15]

The coupling reaction generates only a single isomer with high regioselectivity. The stereochemistry of the *E*-isomer (**4**) has been confirmed from nOe studies, the details of which have been provided in the supporting information. It is noteworthy, that no additives and co-catalysts were necessary for successful completion of the reaction as depicted in **Scheme 6**.

Present Work



Entry	Catalyst (mol%)	Solvent	Temp.	Yield
1.	2.5	Acetone:H_2O(20:1)	RT	50%
2.	5	Acetone:H_2O(20:1)	RT	65%
3.	5	Acetone:H_2O(10:1)	RT	72%
4.	**10**	**Acetone:H_2O(10:1)**	**RT**	**86%**
5.	10	Acetone:H_2O(10:1)	60°C	10%
6.	10	DMF	RT	35%
7.	10	Dry Acetone	RT	5%

Scheme 6. $[CpRu(MeCN)_3]PF_6$ catalyzed coupling reaction and optimization of the reaction condition

Optimization of the reaction conditions as outlined in **Scheme 6** shows the sensitivity of the process to the amount of water present and the concentration of catalyst loading. Thus, 10 mol% catalyst in 10:1 (by volume) acetone:water at room temperature, gave 86% yield of the adduct. Raising the temperature led to decomposition of

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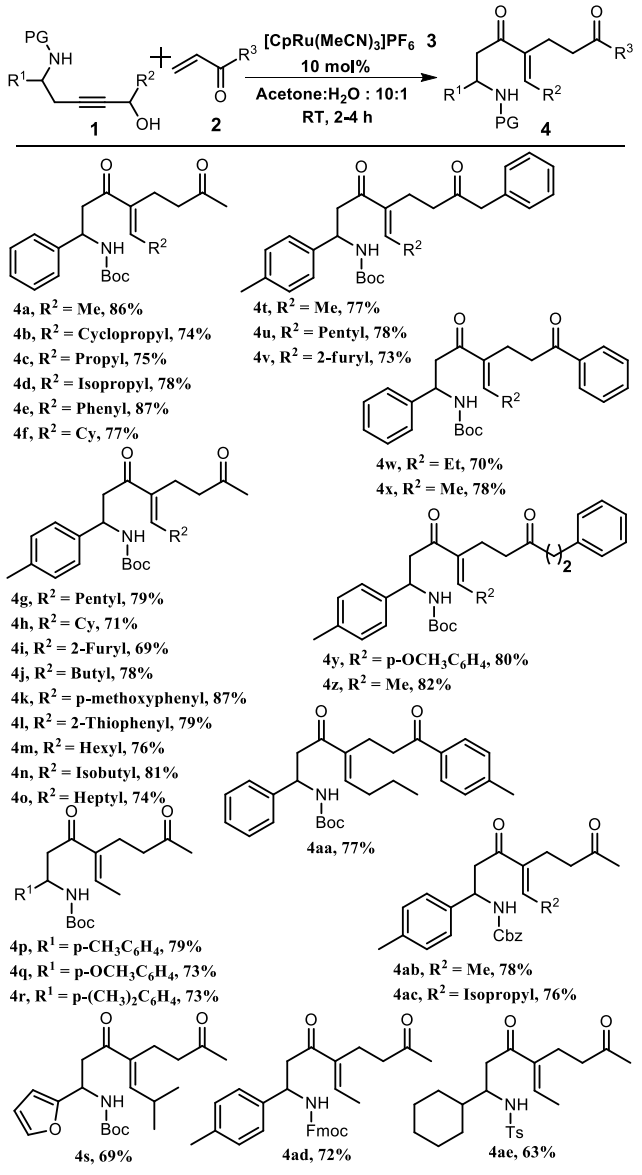
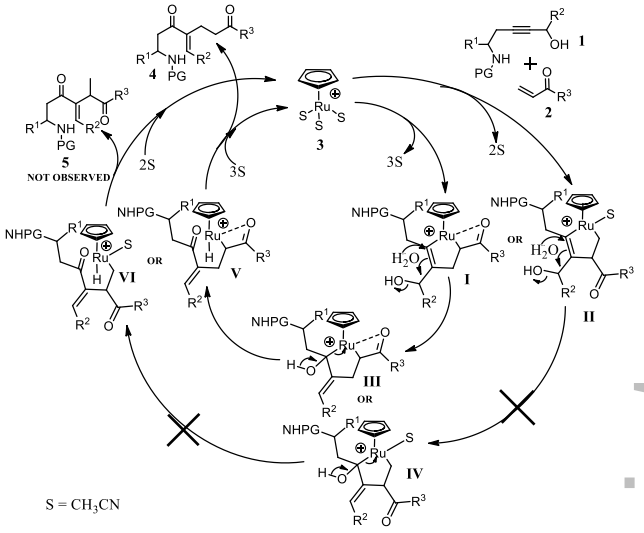
the catalyst with unreacted substrates. Varying the concentration of methyl vinyl ketone *(coupling partner)* did not affect the reaction at all.

The rich substrate scope of the coupling reaction was explored with differently substituted propargyl alcohols in presence of a variety of Michael acceptors. In every case, a satisfactory yield of 63-87% was obtained as a single *E*-geometrical isomer as depicted in **Table 1**.

Table 1. Substrate Scope of Coupling Product

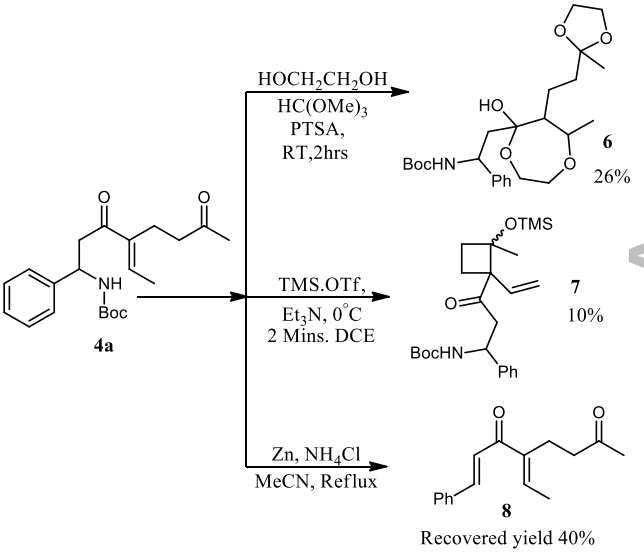


The wide scope of the reaction was demonstrated by its effectiveness in 31 varied examples. From experimental outcome and from existing literature procedures,[16] the presence of water was needed for the reaction which lead us to propose that the reaction proceeded via the formation of a five membered ruthenocycle and a H_2O molecule participated in the catalytic cycle as depicted in **Scheme 7**. The presence of single *E*-geometrical isomer and the structure of the coupling product confirms that the reaction favours a more coordinated ruthenocycle (III) via pathway (I→III→V→4) rather than (II→IV→VI→5).



Scheme 7. Mechanistic Rationale of Coupling Reaction

The completion of the synthesis of the 4-piperidone required a 6-*endo-trig* cyclization of the coupling product. Available acid and base catalytic protocols for the cyclization have been scanty and were limited to disubstituted piperidones only.[17] The *6-endo-trig* cyclization appeared to be a facile one but slowly turned out to a challenging transformation. Attempted PTSA mediated ring closure of the unsaturated ketone **(4a)** delivered a di-ketal **(6)** rather than the cyclised piperidone. Reaction with palladium salts like $Pd(CH_3CN)_2Cl_2$ and $Pd(OAc)_2$ did not prove useful. Reacting with TMS-OTf led to a four-membered carbocycle **(7)**. Performing the reaction in the presence of mild solid phase acidic reagents like Amberlyst resin-15 and silica gel did not afford any desired product. In presence of zinc and NH_4Cl in MeCN, no cyclization product was obtained; rather an elimination product **(8)** was produced as shown in **Scheme 8**.



Scheme 8. Trials for *6-endo trig* cyclization

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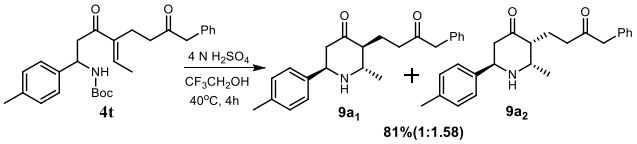
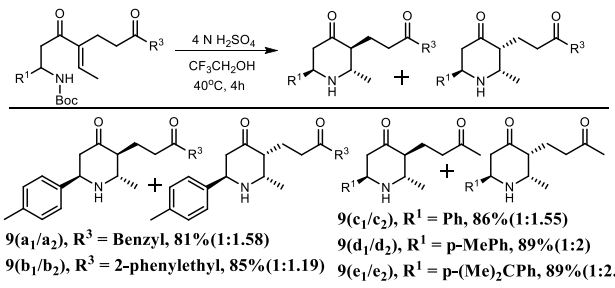
Treatment of the carbamate **(4t)** with 4N H_2SO_4 in trifluoroethanol at 40°C for 4 hrs led to the expected 6-*endo* cyclization and yielded two diastereomers **($9a_1$ and $9a_2$)** in the ratio 1:1.58 with an overall yield of 81% as shown in **Scheme 9**. As observed, the achieved *dr* was not satisfactory, although the isomers could be separated with flash chromatography. The relative stereochemistry was confirmed by multiple nOe studies (details are provided in the supporting information). The (2S,3R,6R), **$9a_2$** isomer was the major product in all cases.



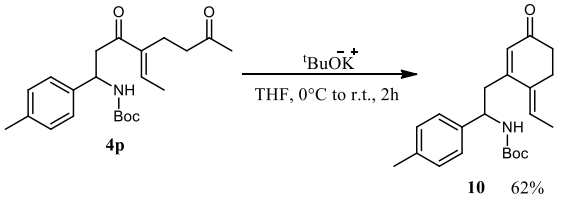
Scheme 9. Acid catalysed *6-endo-trig* Cyclisation

The substrate scope of the cyclized piperidones employing H_2SO_4 is shown in **Table 3**.

Table 3. Substrate Scope for Acid-Catalysed Cyclisation

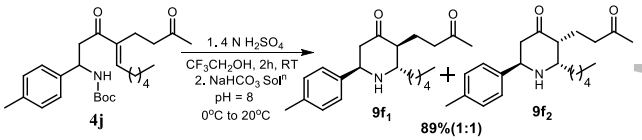


However, a limitation for acid catalyzed cyclization was that the projected *6-endo trig* cyclization happened only when $\mathbf{R^2}$ in the coupling product was a methyl substituent. Repeated attempts to cyclize the coupling product with varied $\mathbf{R^2}$ substituents other than methyl was found to be unsatisfactory under acid catalyzed conditions. Employing the cyclization of carbamate **(4p)** with potassium carbonate gave trace cyclized piperidones in very low yields. Reaction with organic base like Et_3N does not give any cyclized product. Further studies of cyclization of **4j** via enamine type reaction with piperidine, pyrrolidine and L-proline were not fruitful. Use of strong bases like potassium tert-butoxide with **(4p)** did not deliver any N-cyclized product; rather the aldol condensation product **(10)** was obtained as depicted in **Scheme 10**.



Scheme 10. Aldol product

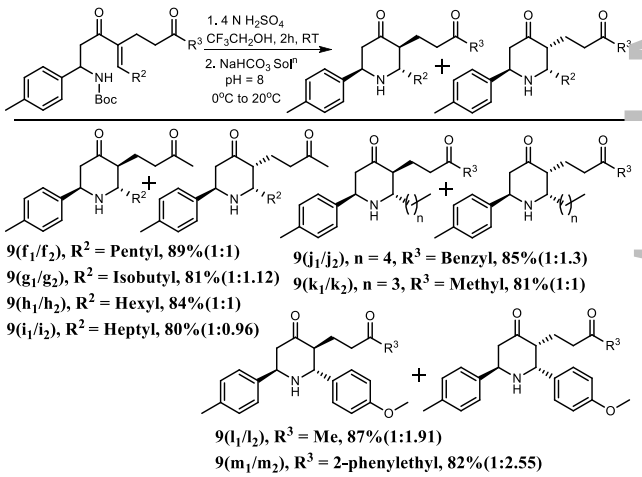
A generalized ring annulation was indispensable for the tri-substituted piperidone synthesis. Albeit, trials on this *6-endo-trig* cyclization employing various Lewis acids and transition metals were found to be unproductive. Interestingly, the carbamate **(4j)** was treated with H_2SO_4 to remove the Boc group followed by basification with saturated $NaHCO_3$ solution with pH maintained at 8 at 0°C to 20°C for 1-6 hours delivered the desired piperidones **($9f_1$ & $9f_2$)** in 89% yield with a 1:1 ratio. The isomers are separated by flash chromatography and the relative stereochemistry was confirmed by multiple nOe studies (details are provided in the supporting information) as depicted in **Scheme 11**.



Scheme 11. Mild base catalysed *6-endo-trig* Cyclisation

The temperature and pH were found to have important effects on the cyclization outcome. Increase of temperature delivered the carbamate eliminated product of the type **8** and increase of pH by addition of strong base gave lower yields of piperidones along with minor amounts of aldol product **10** as in **Scheme 10**. The substrate scope of base catalyzed 6-*endo-trig* cyclization for 4-piperidone synthesis are summarised in **Table 4**.

Table 4. Substrate Scope for Base-Catalysed Cyclisation



It should be noted that the 2,6-stereochemistry achieved was *trans*; whereas, the stereochemistry at C-3 was mixed. These results indicate the conjugate addition of the amine proceeds with high stereoselectivity, but there are no significant effects on the stereochemistry of C-3 protonation. Fortunately, C-3 is easily epimerizable so that either epimer would be obtained in presence of an appropriate base.

In summary, we have reported an atom-economic coupling of varied N-protected amino-2-pent-2-yn-1-ol and Michael acceptors in presence of the second generation catalyst $[CpRu(MeCN)_3]PF_6$ to generate α,β-unsaturated

ketones with high geometrical selectivity. After removing the Boc group, the 6-*endo-trig* cyclization occurred smoothly upon treatment with mild base to deliver tri-substituted-4-piperidones in excellent yields. To the best of our knowledge, a catalytic synthesis of carbon tri-substituted piperidones from an acyclic enone is very rare.[18]

Experimental Section

General procedure for synthesis of coupling product (4) from propargyl alcohol (1) and Michael acceptor (2)

To a well-stirred solution of the propargyl alcohol (**1)** [1 eq] in a (10:1) mixture of acetone and water was added the catalyst $CpRu(CH_3CN)_3PF_6$ (**3**) [10 mol%] and Michael acceptor (**2**) [1 eq] sequentially and stirred at room temperature for 2-4 hrs. Then acetone was evaporated out under vacuum. The reaction mixture was extracted with ether (3 X 5ml) and the organic extract was separated and concentrated under vacuum to give a yellow liquid. The crude yellow liquid was chromatographed with silica gel and eluted with 9:1 [Petroleum ether: EtOAc] to give the coupling product (**4)**.

General procedure for synthesis of piperidones (9) from coupling product (4)

In a well-stirred solution of coupling product (**4**) in trifluoroethanol was added 4 (N) H_2SO_4 and the reaction mixture was stirred at room temperature for 3 hours. Then the reaction mixture was cooled below 20°C and basified upto pH = 8 by dropwise addition of saturated $NaHCO_3$ solution. Then the reaction mixture was allowed to stir at 0°C-20°C for 1-6 hours. After that the organic part was separated by extraction with DCM and dried over anhydrous Na_2SO_4. Evaporation of the organic solvent followed by flash chromatography with silica gel and eluted with 10-30% EtOAc in Petroleum ether afforded the piperidones (**9**).

Acknowledgements

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UPDATE

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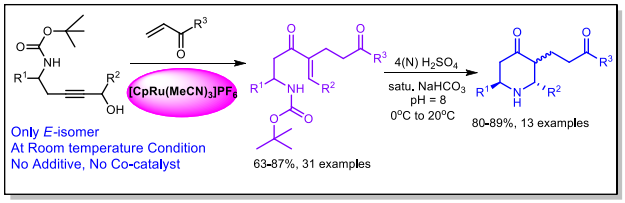

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