Combination iminium, enamine and copper(I) cascade catalysis: a carboannulation for the synthesis of cyclopentenes†

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A one-pot, multistep reaction cascade to cyclopentenes from α,β-unsaturated ketones and propargylated carbon acids through a combination of organocatalysis and transition metal ion catalysis is reported; the reaction cascade is simple to perform, occurs under mild conditions and is broad in scope.

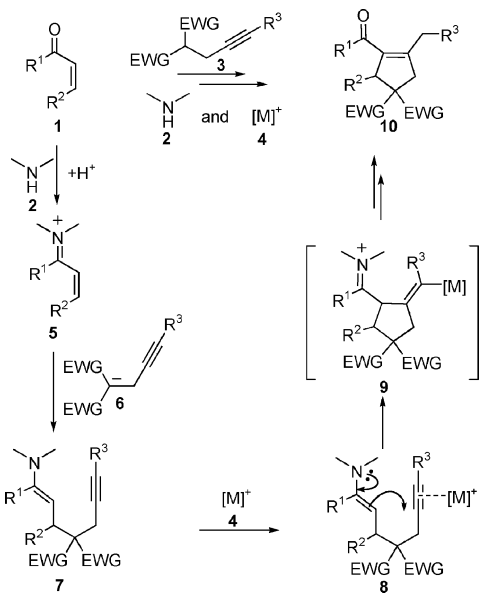
The desire for practically simple and synthetically efficient organic transformations has led to the development of many innovative strategies, concepts and methodologies. One approach is to employ reaction cascades; these can be synthetically powerful allowing rapid and efficient syntheses of complex molecules from relatively simple starting materials by enabling several bond-forming events to occur in the same reaction vessel. Such multistep sequences significantly reduce the drain of resources associated with one-reaction, one-pot approaches. Whereas a myriad of elegant cascade sequences catalysed by a single chemical entity[1] have been described, far fewer reports exist on the use of a combination of more than one mutually compatible catalysts for reaction sequences.[2]

Over the past few years a significant number of cascades involving (single or multiple) amine-based organocatalysts have been reported.[3] These catalysts have allowed the union of multiple reactive functionalities such as electron poor alkenes, aldehydes, ketones, imines, nitroalkanes, and other pro-nucleophiles by providing two key activation modes: iminium activation of α,β-unsaturated carbonyl compounds and enamine activation of carbonyl compounds.[4] These two modes in combination have facilitated some incredibly elegant transformations of relatively simple starting materials to complex stereochemically defined molecular architectures.

Likewise, the field of transition metal or transition metal ion catalysed cascade sequences continues to mature and develop. One area in particular that has witnessed significant interest over the past decade is that of additions to alkyne functionality.[5] More specifically, cascade reactions involving alkyne functionality, wherein 'soft' transition metal ions are employed to provide the necessary activation to trigger the process.[5f]

Confident that mutually compatible cyclic secondary amine organocatalysts and suitably ligated transition metal ion complexes could be identified, we proposed that iminium activation of α,β-unsaturated ketones, enamine activation of ketones and simultaneous metal ion activation of alkynes, could be combined in a cascade sequence constituting a new carboannulation method to cyclopentenes. More specifically, we envisaged that iminium ion activation of α,β-unsaturated ketone **1** to intermediate **5** through condensation with a suitable amine organocatalyst **2** could promote Michael addition of alkyne tethered malonate pro-nucleophile **3** *via* its conjugate base **6**.[6] Bond formation should lead directly to intermediate enamine **7** where the α-carbon is nucleophilic and poised to attack adjacent reactive electrophiles. If this electrophile was indeed an alkynyl functional group activated by metal ion complex **4** then intramolecular carbon–carbon bond formation was anticipated, resulting in an intermediate such as **9**.[7] Protonolysis and hydrolysis would then release the catalysts and the carbocyclic product **10**.[8] With many points of diversity present in the reaction products, this cascade sequence would be a powerful method for both cyclopentene library generation *and* target synthesis (Scheme 1). Herein we present our findings.

Proof of principle studies were carried out using cyclohexenone **11** (1 eq.) and dimethyl propargylmalonate **12** (1.5 eq.) as test substrates (Table 1). Methanol was adopted as the initial solvent owing to its widespread employment in iminium activation of α,β-unsaturated carbonyl compounds.[3b,4,9] Pyrrolidine (20 mol%) was selected as the initial organocatalyst owing to its superior performance in a range of previously reported organocatalytic reactions.[10] With two variables fixed, a range of transition metal salts or complexes [$Cu(OTf)_2$–PPh_3, AgOTf–PPh_3, $Hg(OTf)_2$–PPh_3,



Scheme 1 Concept of the combined iminium, enamine and metal ion catalysis cascade to cyclopentenes.

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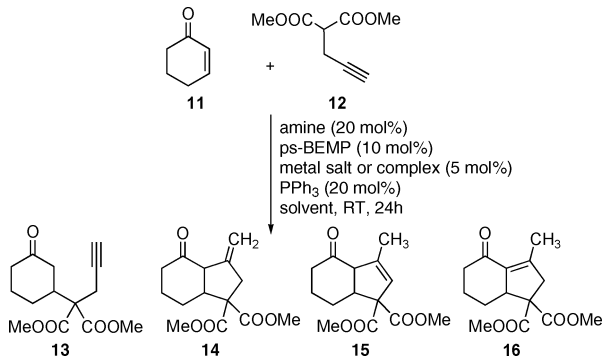
Table 1 Proof of principle, catalyst identification and reaction optimisation studies



Entry	Metal salt	Amine	Solvent	**16** (%)[a]	**13** (%)[a]	**11** (%)[a]
1	$Cu(OTf)_2$	Pyrrolidine	MeOH	91	0	0
2	AgOTf	Pyrrolidine	MeOH	80	0	0
3	$Hg(OTf)_2$	Pyrrolidine	MeOH	32	—	0
4[b]	$Au(PPh_3)Cl$, AgOTf	Pyrrolidine	MeOH	86	0	0
5[b]	$Pd(PPh_3)_4$	Pyrrolidine	MeOH	71	0	0
6	$Cu(OTf)_2$	Piperidine	MeOH	21	18	16
7	$Cu(OTf)_2$	*n*-Propylamine	MeOH	13	0	22
8	$Cu(OTf)_2$	Pyrrolidine	CH_2Cl_2	35	0	27
9	$Cu(OTf)_2$	Pyrrolidine	$CHCl_3$	27	0	38
10	$Cu(OTf)_2$	Pyrrolidine	Toluene	21	16	48
11	$Cu(OTf)_2$	Pyrrolidine	THF	9	0	63
12	$Cu(OTf)_2$	—	MeOH	0	8	25

[a] ^{1}H NMR yield measured using an internal standard. [b] Additional PPh_3 (20 mol%) was not added to the reaction mixture.

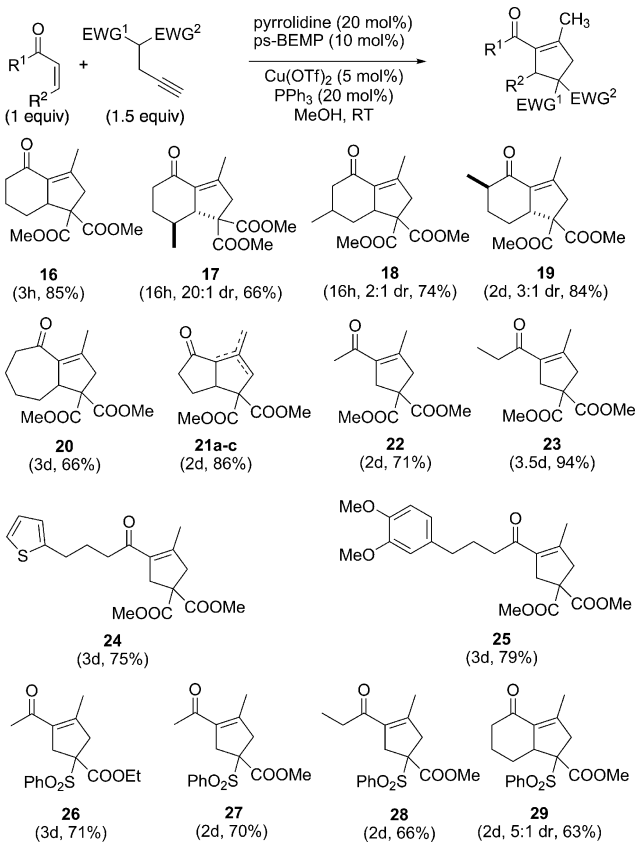
$Au(PPh_3)Cl$–AgOTf and $Pd(PPh_3)_4$] was screened for performance in the cascade at room temperature for 24 h. In each reaction ps-BEMP (10 mol%) was added to quench any residual protic acids present in the commercial metal ion salts.[5f,11] The results are presented in Table 1 (entries 1–5).

Pleasingly, in all of these initial experiments the dominant reaction product was the conjugated bicyclic enone **16**. Cyclohexenone **11** could not be detected in any of the crude reaction mixtures, confirming that in all cases the reactions had gone to completion. Michael adduct **13** could not be detected in any case, suggesting that the cyclisation stage was faster than the Michael addition. Product isomers **14** and **15** could not be detected in any of the crude reaction mixtures. Although AgOTf and $Au(PPh_3)Cl$–AgOTf were effective catalysts in the cascade, the best result in terms of yield employed $Cu(OTf)_2$ in the presence of triphenylphosphine (entry 1). Accordingly, further investigations were carried out using this catalyst–ligand combination. Changing pyrrolidine to piperidine or *n*-propylamine led to dramatically diminished reaction yields (entries 6 and 7) whereas employing any other typical reaction solvent in the presence of pyrrolidine led to significantly decreased reaction rates (entries 8–11). A control experiment, where pyrrolidine was omitted, confirmed the importance of the amine organocatalyst in both the Michael addition *and* carbocyclisation steps (entry 12); although the strong base ps-BEMP[12] catalysed the slow formation of **13**, no bicycle **16** was observed, thus the postulated intermediacy of an iminium ion (**5** in Scheme 1) in the Michael addition step and an enamine (**7** in Scheme 1) in the carbocyclisation step was supported.

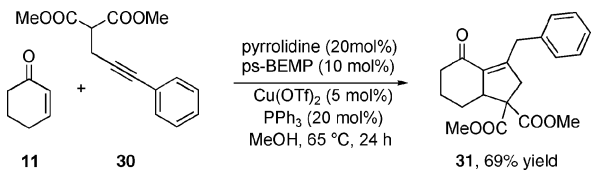
With proof of principle established and the optimal reaction conditions identified, the scope of the cascade was surveyed by probing changes to the α,β-unsaturated ketone and the pronucleophile (Scheme 2). A methyl substituent was tolerated at the γ, δ, and ε positions of the cyclohexenone Michael acceptor and high diastereoselectivity was observed in the formation of **17**. Cycloheptenone and cyclopentenone gave rise to the 7,5- and 5,5-bicyclic ring systems respectively. Interestingly, in the latter case a mixture of isomeric alkene products **21a**–**c** was isolated, with the major being the non-conjugated endocyclic alkene. Methyl and ethyl vinyl ketones gave rise to the respective monocyclic cyclopentenes **22** and **23**. Likewise longer chain alkyl vinyl ketones carrying spectator aromatic rings gave rise to cyclopentenes **24** and **25** in good yields in both cases. α-Sulfonyl esters bearing the terminal alkynyl group also partook in the reaction to afford cyclopentenes **26**–**29**. In the case of cyclohexenone as the Michael acceptor NMP (*N*-methylpyrrolidinone) was identified as a better reaction solvent than methanol and a 5 : 1 diastereomeric ratio of reaction product **29** was isolated.

To further investigate the scope of the reaction cascade, arylated alkyne **30** was synthesised and tested for performance in the reaction. Although the reaction was sluggish at room temperature, pleasingly in methanol at 65 °C for 24 h the desired bicyclic product **31** was formed as a single isomer in 69% yield (Scheme 3).

In the presence of excess triphenylphosphine, Cu(II) salts are known to reduce to Cu(I) complexes such as $(Ph_3P)_3CuX$ where X is the counterion of the starting salt.[13] Moreover, the ability of Cu(I) to activate triple bonds towards nucleophilic attack has already been demonstrated.[14] Therefore we postulate that the catalytically active metal ion species responsible for alkyne activation in our reaction mixture is $(Ph_3P)_3CuX$ (where X is



Scheme 2 Scope of the combination catalysis cascade to cyclopentenes.



Scheme 3 Combination catalysis cascade of a non-terminal alkyne.‡

either OTf or OMe). This hypothesis was supported when a mixture of $(Ph_3P)_3CuCl$[15] and AgOTf was tested for performance in the cascade and a comparable result (3 h reaction time, 80% yield) with respect to the $Cu(OTf)_2$–PPh_3 system was obtained. Furthermore, ^{31}P NMR experiments of reaction systems using $Cu(OTf)_2$–PPh_3 or $(CuOTf)_2{\cdot}C_6H_6$–PPh_3 identified complexes common to both (see ESI for details†).

In summary, a mutually compatible combination of pyrrolidine and $Cu(OTf)_2$–PPh_3 catalysts has been identified that promotes a new carboannulation to cyclopentene products from α,β-unsaturated ketones and propargylated carbon acids. Initiated through a Michael addition to the iminium ion activated enone, the enamine intermediate is poised to undergo C–C bond formation with the copper(I) activated alkyne. Subsequent protonolysis, hydrolysis and isomerisation provide the cyclopentene products in moderate to good yields. Further studies to widen the range of substrates amenable to this type of catalysis cascade are under investigation and the results will be reported in due course.

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‡ Arylated alkyne **30** was synthesised by a Sonogashira coupling of dimethyl propargylmalonate **12** with iodobenzene (see ESI for details†).

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