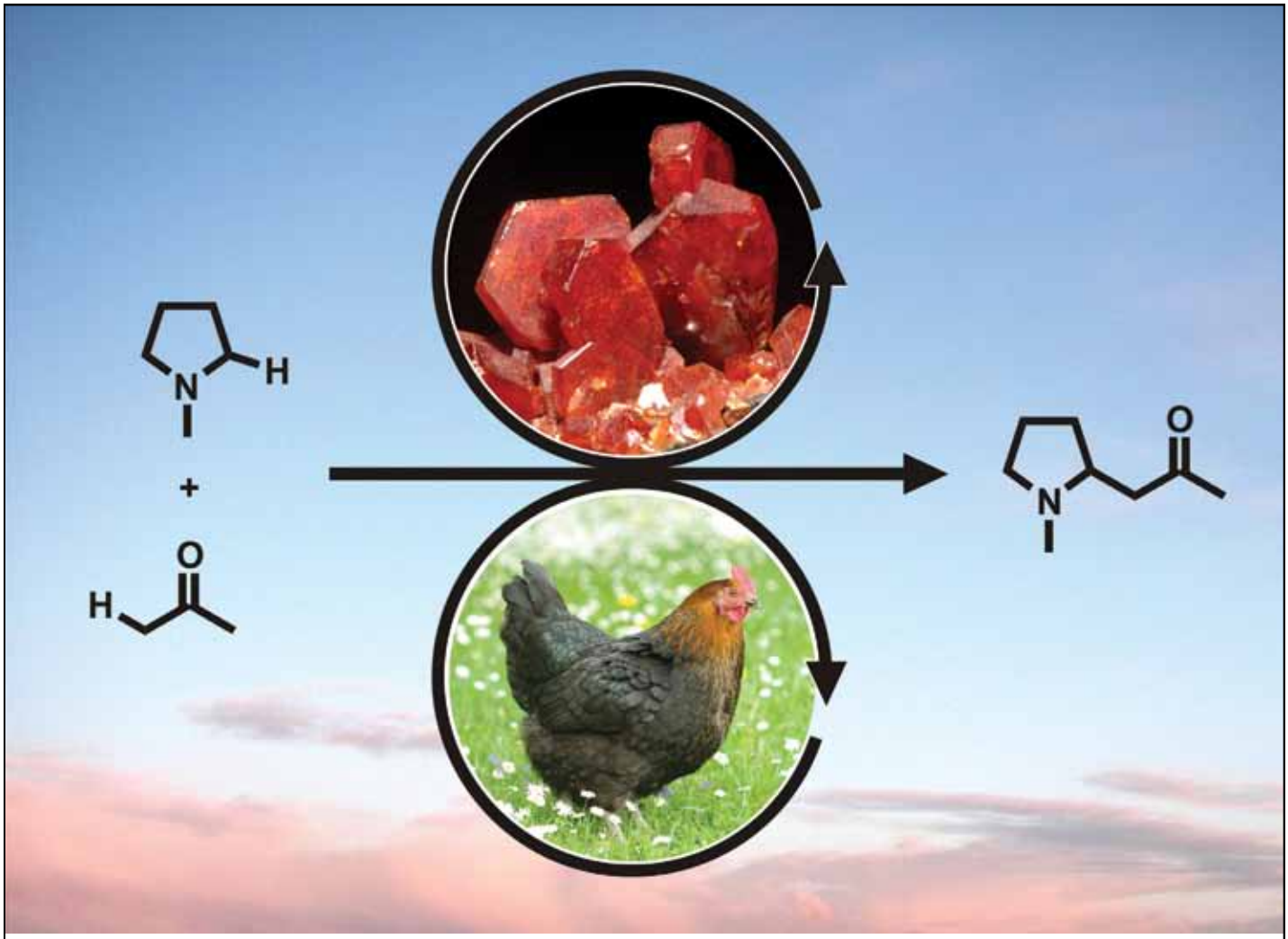

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Title: Oxidative coupling of amines and ketones by combined vanadium- and organocatalysis

The back cover displays the synthesis of the natural product hygrine by dual catalysis: vanadinite crystals represent oxidative vanadium catalysis and the chicken stands for catalysis with proline, a natural amino acid which can be isolated from chicken feathers.

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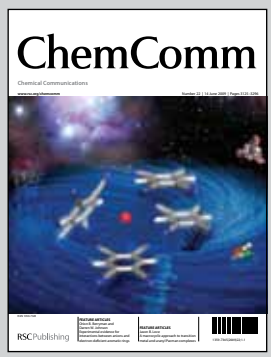

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Oxidative coupling of amines and ketones by combined vanadium- and organocatalysis†

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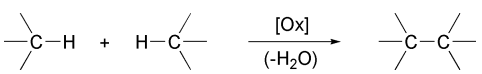
Received (in Cambridge, UK) 21st January 2009, Accepted 17th February 2009
First published as an Advance Article on the web 17th March 2009
DOI: 10.1039/b901282f

The combination of vanadium- and organocatalysis allows for the direct oxidative coupling of cyclic tertiary amines with non-activated ketones without the need for preformed leaving groups.

Oxidative coupling can be an elegant way to form new carbon–carbon bonds without the need of special leaving groups by formally breaking two carbon–hydrogen bonds and coupling the fragments.[1] As a net oxidation of the substrates occurs, an oxidant is required, typically producing water as the only byproduct (Scheme 1). These reactions can be very atom economic and also faster than other routes that require multiple steps and functionalisations.

We became interested in utilising oxidative coupling reactions of amines and carbonyl compounds as an alternative to Mannich reactions, furnishing valuable structural motives that occur in natural products and pharmaceuticals. The oxidative functionalisation of amines in the α-position has been investigated for some time.[2] In most of these cases, iminium ions are thought to be the key intermediate; a subsequent reaction with good nucleophiles then furnishes the products.[3] Li and co-workers have recently made important progress in this field by significantly expanding the scope of these reactions, generally using copper catalysts together with organic peroxides[1b,4] or oxygen.[4d] In all these examples, the carbonyl compounds that could be coupled with the amines exhibited considerable nucleophilicity, a noteworthy exception are enones that were activated in a Baylis–Hillman-type fashion.[4c] The direct coupling with non-activated simple ketones has not been achieved so far.

To overcome this limitation, we planned to use a secondary amine as an organic cocatalyst to activate ketones in the form of a nucleophilic enamine intermediate.[5] Subsequent reaction with iminium ions formed by oxidation of the amine would then lead to the product. To test our strategy, we tried to perform the coupling of tetrahydroisoquinoline **1** with acetone in the presence of a metal catalyst, *tert*-butyl hydroperoxide (TBHP) as oxidant and L-proline as an inexpensive and reliable organocatalyst (Table 1).



Scheme 1 Carbon–carbon bond formation by oxidative coupling.

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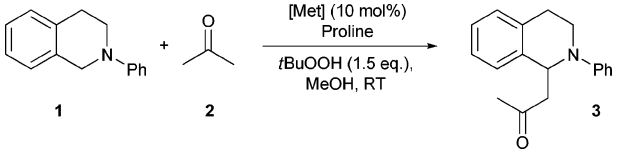
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b901282f
‡ A. S. and D. S. contributed equally to this project.

Table 1 Screening of metal catalysts for the oxidative coupling of amine **1** with acetone[ab]



1 2 3

Entry	Met	Proline/ mol%	*t*/h	Conversion of **1** (%)	Yield[c] (%)
1	$CuCl_2$	10	12	Full	<5
2	$Cu(acac)_2$	10	96	Full	43
3	$FeCl_3 \cdot 6H_2O$	10	8	Full	23
4	$Fe(acac)_3$	10	12	Full	28
5	$Co(acac)_2$	10	24	Full	41
6	$VO(acac)_2$	10	24	Full	69
7	$VO(acac)_2$	—	72	<5	0
8	—	10	24	50	6

[a] Reaction conditions: amine (0.12 mmol), ketone (0.60 mmol), metal catalyst (0.012 mmol), L-proline (0.012 mmol), TBHP–decane (0.18 mmol), MeOH (1.0 ml), RT. [b] acac = acetyl acetonate. [c] Isolated yield.

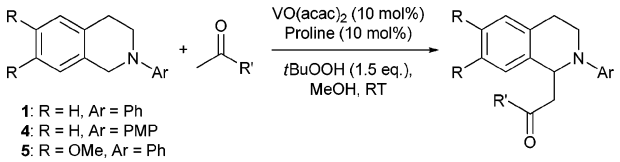
With copper chloride, only traces of the desired product were formed, while a moderate yield (43%) was obtained after four days using the corresponding acetyl acetonate (acac, entries 1 and 2). Potentially, the chelating acac ligands hinder a coordination of the metal with proline, which could lead to a deactivation of both catalysts. Copper(II) is known to form a stable complex with proline[6] and we could show that addition of proline deactivates oxidative copper catalysis in the coupling of naphthol to 1,1′-bis-2-naphthol.[7]

Iron and cobalt catalysts gave faster conversions but not higher yields (entries 3–5). This was achieved with $VO(acac)_2$, forming **3** with 69% yield after one day (entry 6). No product was formed without the cocatalyst proline and only trace amounts without $VO(acac)_2$ (entries 7 and 8), indicating the success of the dual catalysis concept. The reactions generally produced several unidentified decomposition products, which explains the moderate yields of the desired product even in the cases of high conversion. Other oxidants than TBHP gave lower yields and no reaction occurred with elemental oxygen.

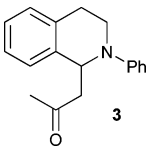
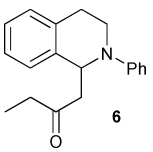
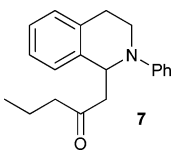
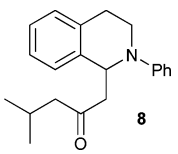
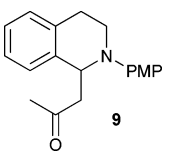
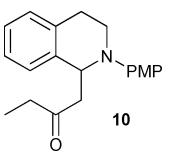
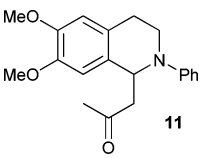
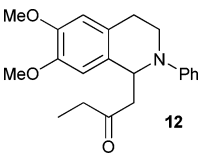
Optimisation of the reaction conditions led to the establishment of 10 mol% $VO(acac)_2$ and 10 mol% L-proline, methanol as the solvent and the use of 1.5 equivalents of TBHP as the oxidant. Several tetrahydroisoquinolines could be coupled with a number of acyclic aliphatic ketones (Table 2).

Interestingly, the coupling always occurred at the non-substituted α-position of the ketone, in contrast to the

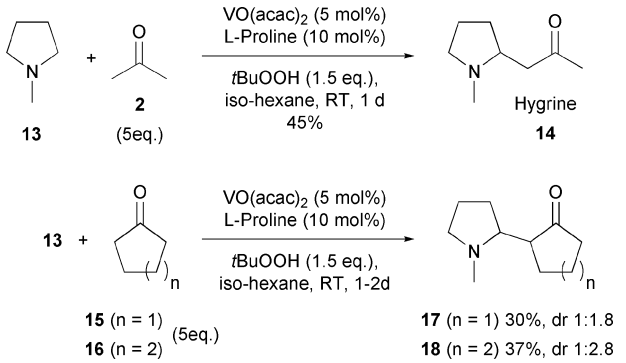
Table 2 Oxidative coupling of tetrahydroisoquinolines with ketones by dual vanadium- and organocatalysis[ab]



1: R = H, Ar = Ph
4: R = H, Ar = PMP
5: R = OMe, Ar = Ph

Entry	Amine	R′	Product	*t*/d	Yield[c] (%)
1	**1**	Me	 **3**	1	69
2	**1**	Et	 **6**	1	65
3[d]	**1**	*n*-Pr	 **7**	1	41
4	**1**	*i*-Bu	 **8**	3	32
5	**4**	Me	 **9**	1	51
6	**4**	Et	 **10**	1	40
7	**5**	Me	 **11**	1	65
8	**5**	Et	 **12**	1	36

[a] Reaction conditions: amine (0.12 mmol), ketone (0.60 mmol), $VO(acac)_2$ (0.012 mmol), L-proline (0.012 mmol), TBHP–decane (0.18 mmol), MeOH (1.0 ml), RT, 1–3 d. [b] PMP = *p*-methoxyphenyl. [c] Isolated yield. [d] Solvent DMSO, 2.0 eq. TBHP.



Scheme 2 Synthesis of hygrine and derivatives by oxidative coupling with *N*-methyl pyrrolidine **13** (dr = diastereomeric ratio, determined by ^{1}H-NMR).

outcome of most organocatalytic reactions.[5] Accordingly, we were not able to obtain products with ketones without an α-methyl group, possibly due to steric reasons.

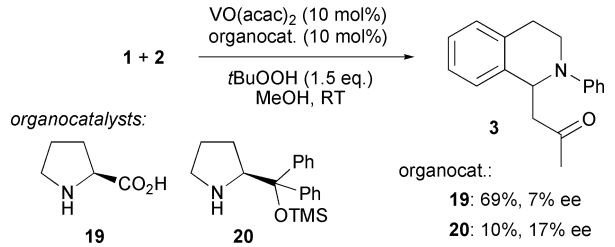
Next, we turned our attention to other cyclic tertiary amines. *N*-Methyl pyrrolidine **13** proved to be another good substrate, despite giving lower yields than **1**. To our delight, the reaction with acetone proceeded well to yield hygrine **14**, a natural product that is a biochemical precursor for several other alkaloids.[8] The modest yield of only 45% is counterbalanced by the fact that our methodology provides a direct one-step synthesis of hygrine, the shortest total synthesis reported,[8,9] using simple and readily available starting materials (Scheme 2).

Lower loadings of $VO(acac)_2$ (5 mol%) could be used without influence on the yield and isohexane proved to be the best solvent for this substrate which failed with amine **1**, probably because of its low solubility. We were unable to obtain more than traces of the coupling products with other open-chain ketones except acetone. Nevertheless, we were able to isolate the coupling products with cyclic ketones. In contrast to the reactions with **1** depicted in Table 2, slow formation of the products with amine **13** occurred even without the organocatalyst. This could be due to base-catalysed enolisation of the ketones with the more basic **13**.

Despite the use of an enantiopure organocatalyst, proline, nearly all the products isolated were racemic. This can be rationalised by the facile racemisation of β-amino-ketones. Hygrine **14** is known to racemise very fast in basic conditions and even without added base racemisation can occur within minutes to hours.[9] Not surprisingly, we could only obtain racemic **14**. However, enantiopure hygrine would still be accessible by resolution with tartaric acid.[9]

Non-racemic products were achieved with tetrahydroisoquinoline **1**, albeit with very low enantioselectivities. For example, **3** was produced with 7% ee catalysed by L-proline; screening of various other chiral organocatalysts revealed Jørgensen-type catalyst **20**[10] as the most stereoselective with a product ee of 17% but poor yields (Scheme 3).

Further attempts of asymmetric catalysis by using chiral vanadium complexes all failed, only yielding racemic products. We found that enantiopure **3**, obtained by preparative HPLC, slowly racemized under the reaction conditions (see ESI†).

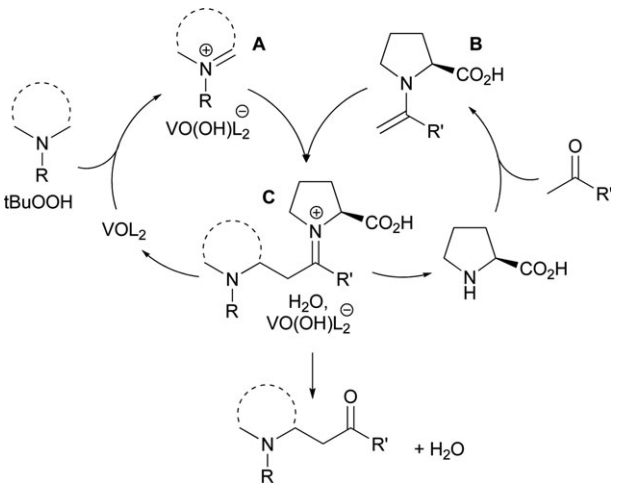


Scheme 3 Results of asymmetric reactions using chiral organocatalysts.

This could help to explain the low enantioselectivities observed in the product. Obviously, asymmetric oxidative coupling reactions with tertiary amines[11] remain a challenge, as amino-carbonyl compounds have previously only been made racemic and the best ee achieved with other coupling partners is 74% in an alkynation.[12] Although the use of enantiopure proline seems superfluous in non-asymmetric reactions, it still is the cocatalyst of choice in this reaction. Its high activity, low price and ease of use as a bench-stable crystalline solid make it superior to other organocatalysts we have tested.

Since both the formation of amine *N*-oxides from tertiary amines[13] and their conversion to iminium ions[14] are reported to be catalysed by vanadium complexes, we initially assumed that the reaction mechanism involved amine *N*-oxides as key intermediates. However, the preformed *N*-oxide of **13** failed to react under our reaction conditions. Also, it could not be detected as an intermediate, even when the reaction was performed in the absence of a ketone and proline. Alternatively, iminium ions could be formed by a radical mechanism, involving a stepwise removal of electrons and a proton. The existence of radical intermediates is supported by the fact that the synthesis of hygrine failed if one equivalent of the radical inhibitor 2,4,6-tri-*tert*-butyl phenol is added.

As a working model, we propose a dual catalytic cycle involving an iminium ion **A**, formed by oxidation through a radical pathway from the substrate amine, and a nucleophilic enamine **B**, formed from the ketone and proline, which attacks the iminium ion. Intermediate **C** is then hydrolysed to give the product and reform both catalysts (Scheme 4). Accordingly, the reaction can be considered an "oxidative Mannich reaction".[15]



Scheme 4 Mechanistic proposal (L = acetyl acetonate).

Despite the modest yields and restricted substrate scope, this reaction significantly enhances previous methodologies in both metal- and organocatalysis. By using an organic cocatalyst, simple non-activated ketones become accessible substrates for oxidative coupling reactions.[16] By utilising oxidative vanadium catalysis, cyclic amines become accessible for Mannich-type reactions that are usually the domain of open-chain imines. Further studies to extend the scope of these reactions are ongoing in our laboratory.

We are grateful for financial support from the Alexander von Humboldt-foundation (research fellowship to D. S.) and from Prof. Benjamin List. We thank Esther Böß for the synthesis of some starting materials.

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