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Synthesis of functionalized chromene and spirochromenes using L-proline-melamine as highly efficient and recyclable homogeneous catalyst at room temperature

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ABSTRACT

An efficient and recyclable homogeneous catalyst is developed using commercially cheap L-proline and melamine for the synthesis of chromenes and spirochromenes (spirooxindoles) *via* multicomponent reactions at room temperature. Systematic studies were conducted in order to achieve desired reactivity and recyclability of the catalyst using various α-amino acids and aromatic amines as donor-acceptor pairs. Among the screened combinations, L-proline and melamine (3:1 ratio; 3 mol% on total weight) was found to be best catalyst to give the desired products with excellent yields (up to 99%) in very short times (1–15 min) at room temperature in DMSO as solvent. The catalyst was recovered by adding EtOAc and reused up to 5 cycles without losing the catalytic activity.

Homogeneous catalysis enjoys the advantage of product selectivity and yields over heterogeneous catalysis depending on the number of active sites in the catalyst. However, the separation of the product, loss of the catalyst and regeneration of the catalyst from the reaction mixture (which require tedious processes, thus may not be suitable for sensitive products) is the main limitation of homogeneous catalysis.[1a–c] Because of this, designing the recyclable homogeneous catalysts with high activity, selectivity and easy separation from the products is always a challenge. In this regard, different approaches were adopted for the development of recyclable homogeneous catalysts. The use of homogeneous catalyst with covalently, non-covalently bonded or immobilized silica or insoluble polymer/resin is most common method for this purpose.[1a,2a] Along with these, the use of organometallic complex and metallodendrimes,[2b,2c] transforming a homogeneous catalyst into heterogeneous catalyst using nanoparticles,[2d] solvent/temperature dependent solubility of the catalyst during and after the reaction, (thermomorphic solvent systems),[1a,2e] precipitation of the catalyst after completion of the reaction,[2f] exposure to UV radiation,[2g] metals complexed with macromolecules (self supported),[2h] tagged catalyst with ionic liquids,[2i] are known in the literature.

L-proline mediated reactions often take more time for completion and give poor stereoselectivity. These limitations have been addressed by using additives,[3a] co-catalysts,[3b] incorporating covalently bonded functional groups,[3c] host-guest complexes, and by modular designed organocatalysts.[3d] As a result, last couple of decades have witnessed the use of L-Proline and its derivatives as organocatalysts for different types of reactions[4a,b] and synthesis complex products/biologically important compounds.[4c,d] Along with these, L-proline has been used for multicomponent reactions (MCRs) for the preparation of functionalized pyrans, dihydropyridines, pyridones, pyrazolo[3,4-*b*]quinolines, 4H-pyrano[2,3-*c*]pyrazoles, naphthyridines, dicoumarols etc.[5]

2-Amino-4H-chromene-3-carbonitriles (chromenes)[6] and 2′-amino-2-oxospiro[indoline-3,4′-pyran]-3′-carbonitrile (spiro chromenes/spirooxindoles)[7] are known to show many biological properties including anticancer, antioxidant and antimicrobial, inhibitors of excitatory amino acid transporters etc. Currently, these compounds are prepared by MCR approach using different catalysts like urea,[8a] potassium phthalimide,[8q] organic bases (TEA, DBU, DABCO, DMAP),[8b–e] inorganic salts ($CaCl_2$,[8h] NH_4Cl,[8j] tungstic acid,[8l] cellulose–$HClO_4$,[8i] $NbCl_5$), alternative reaction media (chitosan/ionic liquid,[8k] $BnN(Et)_3Cl$ surfactant,[8n] sulfated choline based heteropolyanion salt,[8o] micellar media[8p]), nanomaterials (nano-organocatalyst,[8f,8g] γ-Fe_2O_3 nano particles[8m]) amino acids (cysteine,[8r]) and catalyst free[8s,8m] conditions. Along with these

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methods, L-proline and supported proline derivatives[9] also been used for the synthesis of purpose (Fig. 1). However, many of these methods (including L-proline) involve the use of temperature, require more time for completion of reaction and limit to three or four types of nucleophiles in both simple chemomene and spirooxindole case.Fig. 2

Though the use of small molecules as additives or co-catalysts is known concept,[3b] the use of commercially available small organic molecules (other than L-proline) as recyclable homogeneous catalysts is rare.[10] Thus, considering the biological importance chromenes, recyclable homogeneous catalysis and in continuation with our efforts in developing simple synthetic methods,[11] here in we report L-proline-melamine combination as highly efficient recyclable homogeneous catalyst for the synthesis of chromenes and spirochromenes *via* MCR approach. Towards this, we envisaged the use of commercially available small organic molecules with hydrogen bonding donor-donor and donor-acceptor sites as additives in combination with α-amino acid derivatives.[3,12] In order to achieve the desired reactivity, active catalyst systems, initially the catalyst systems were prepared by mixing L-proline (**1a**) with different aromatic and heteroaromatic amines (**2a**–**2e**) in MeOH (RT, overnight). Evaporation of the solvent gave active catalysts as white powder (see ESI for detailed procedure) which were used (3 mol%) for multicomponent reaction of isatin (**3a**) with dimedone (**4a**) and malononitrile (**5a**) to desired spirochromene (**6a**) in 50–70% yield (Scheme 1;Table 1; entries 1–10). It is interesting to note that all the catalyst systems are giving the desired product with moderate yields compare to the reaction of L-proline (30 mmol) (Table 1; entry 1). Also, entry 4 indicate that the structural features (1,3-relationship of the nitrogen; charged species of pyridinium ion) of the aromatic amines are important for faster kinetics of the reaction. Considering this, further investigation was continued using different heteroaromatic amines (**2f**–**2h**) and guanidine (**2i**). Among these, the combination of L-proline (**1a**) and 2-aminopyrazine (**2f**)/guanidine (**2i**) are slightly better in terms of reactivity which may be due to distant donor-acceptor

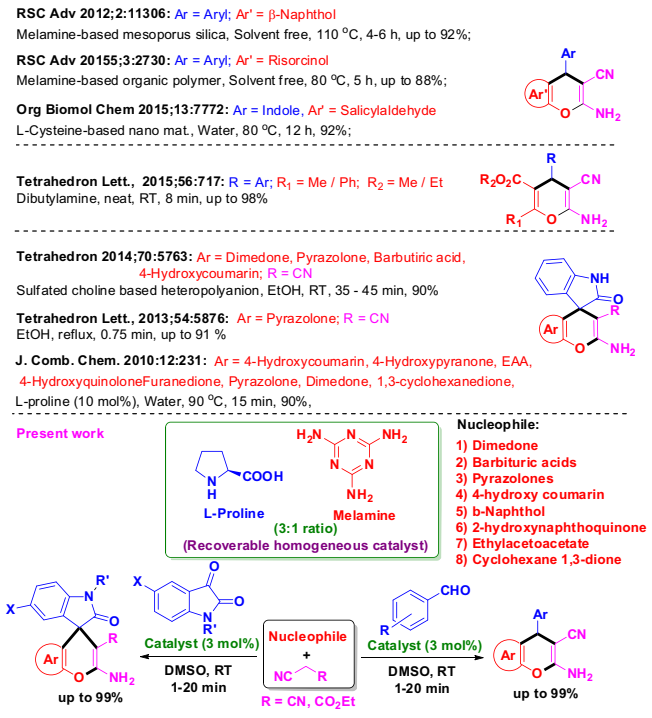


Fig. 1. Closely related literature methods for the synthesis of chromenes and spirochromenes and present study.

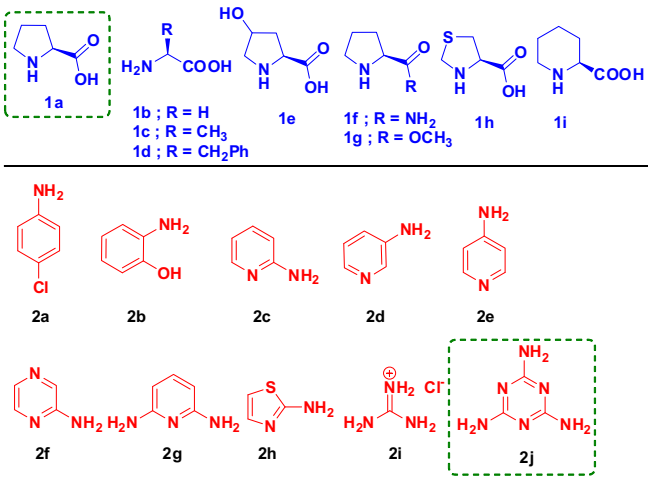
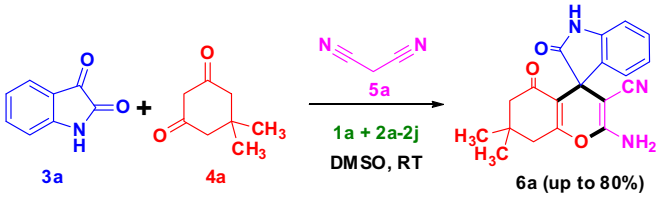


Fig. 2. Different α-amino acids and aromatic amines used in the present study for the development of recyclable homogeneous catalyst.



Scheme 1. Catalyst screening for the multicomponent reaction of isatin (**3a**), dimedone (**4a**) and malononitrile (**5a**).

Table 1
Screening of the catalysts for the MCR of isatin (**3a**) dimedone (**4a**), and malononitrile (**5a**).

S. No.	Catalyst combination	Reaction time (h)	Isolated Yield (%)[a]
1	1a (30 mol%) + no additive	24	25
2	1a + 2a (1:1)	5	60
3	1a + 2b (1:1)	4	65
4	1a + 2c (1:1)	4	70
5	1a + 2d (1:1)	5	60
6	1a + 2e (1:1)	6	50
7	1a + 2f (1:1)	3	80
8	1a + 2g (1:1)	8	60
9	1a + 2h (1:1)	5	75
10	1a + 2i (1:1)	3	80
11	**1a + 2j (1:1)**	**40 min**	**85**
12	**1a + 2j (2:1)**	**25 min**	**90**
13	**1a + 2j (3:1) (3 mol%)**	**5 min**	**99**
14	Only 2j	24	ND
15	2b + 2j	6	70
16	2c + 2j	24	30
17	2d + 2j	24	35
18	2e + 2j	24	20
19	2f + 2j	24	Trace
20	2g + 2j	24	ND
21	2h + 2j	24	ND
22	2i + 2j	24	ND
23	1a + 2j (in water)		Trace

Bold values used to identifying the best reaction conditions.
Reaction conditions: [a]All the reactions were performed at 1 mmol scale using 3 mol % of the catalyst in DMSO solvent at RT and given as isolated yields.

atoms and their ratio/increased pKa values of catalyst system because of the presence of extra nitrogen.

Melamine **2j** (1,3,5-Triazine-2,4,6-triamine) with pKa 5 and 66% nitrogen content is a unique molecule that has hydrogen donor-acceptor-donor sites (donor to donor distance of 4.8 A° units) to