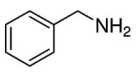
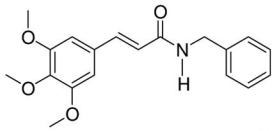
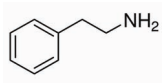
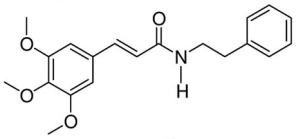
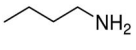
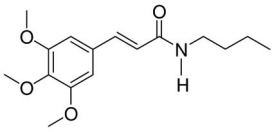
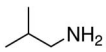
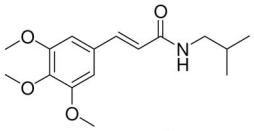
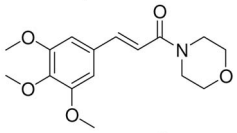
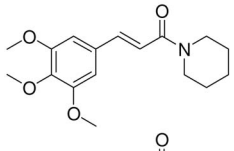
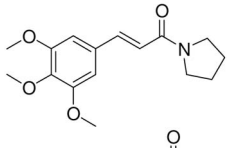
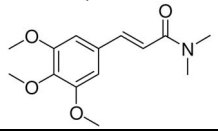
Unprecedented intermolecular transamidation reaction of piplartine

Piplartine reacts easily with primary as well as secondary alkyl amines to afford carboxamides in the presence of magnesium bromide etherate. The reaction proceeds via alcoholysis of imide bond and simultaneous attack of amine, and features a rare example of an intermolecular transamidation reaction between an imide and amine pair under mild conditions. Transamidation is a useful tool in synthetic organic chemistry. However, direct transamidation is known to be a difficult reaction and it is restricted to special conditions and requirements such as ring expansion of lactams[1–4] and oxosultams[5], lower carboxamides[6,7], intramolecular processes[8–12], activated amides[13–16], catalytic conditions (enzymatic[17,18] and Lewis acid catalysis[19,20]), or high temperatures[21] and critical pH[22]. Amide exchange has also been described in solid-phase synthesis[23]. High temperatures (>250°C) can promote chemical exchange in amide polymers or polymer/amine mixtures[24–28], and stoichiometric quantities of $AlCl_3$ mediate transamidation between amine and carboxamide pairs at 90°C (refs 29 and 30). Enzyme-mediated transamidation has been achieved, although the reaction has limited substrate scope and requires long reaction times[31–33].

The recent exciting developments in dynamic covalent chemistry[34] suggest that facile amide exchange reactions, which are presently unknown, would enable the synthesis of new important amide-based molecules and polyamide materials under equilibrium-controlled conditions. The importance of secondary amides in synthetic and biological polymers led us to focus our attention on this class of substrates. Recently, L-proline-catalysed transamidation of carboximides with amines was reported under solvent-free conditions in a sealed tube[35]. Herein, we report a novel transamidation of a non-activated carboximide, specifically piplartine, with primary and secondary alkylamines under mild reaction conditions (Scheme 1) that represents an important step in this direction.

Successful application of catalytic transamidation in dynamic covalent chemistry will require facile exchange in the

Table 1. Magnesium bromide etherate-mediated transamidation of piplartine–amine pairs

Entry	Amine[a]	Time (h)	Product[c]	Isolated yield (%)
1		5		90
2		7		85
3		10		70
4		9		78
5		5		85
6		8		70
7		8		75
8		10		78

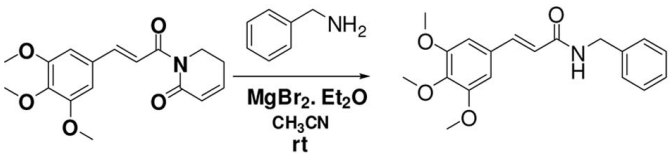
absence of an intrinsic thermodynamic driving force. We therefore shifted our attention to approximately thermoneutral exchange reactions between alkylamines and imide, specifically piplartine. The carboximide group is chemically robust and generally requires harsh conditions or highly evolved enzymes to react. There are few examples on imides that too restricted to few reagents as the poor reactivity of the imide bond. A thiourea-catalysed asymmetric Michael addition of activated methylene compounds such as malononitrile, methyl α-cyanoacetate and nitromethane could be employed as a nucleophile to give the Michael adducts in good to excellent yields with up to 93% has been reported and the reaction is limited to malononitrile due to the poor reactivity of imide bond[36–39]. In a preliminary experiment, we studied the behaviour of piplartine **1** (0.315 mmol) with benzyl amine (0.0405 mmol) in the presence of magnesium bromide etherate (0.25 mmol) at room temperature; the expected Michael adduct was not obtained and the unexpected transamidation product was exclusively obtained in excellent yield (Scheme 1, Tables 1 and 2, entry 1) within 5 h. Product **1c** was characterized by ^{1}H and ^{13}C NMR spectroscopy. This experiment, along with NMR analysis, constitutes unequivocal evidence for the structure of carboxamides and confirms the proposed transamidation reaction. Encouraged by this, other primary amines such as phenethyl amine, *n*-butyl amine and isobutyl amine (entries 2–4) were treated with piplartine under the same experimental conditions and the corresponding transamidated products were isolated in excellent yields within 5–12 h.

Surprisingly, when the reaction conditions were changed and piplartine **1** was treated with the alkyl amines (morpholine, isobutylamine, piperidine and pyrrolidine) in methanol at room temperature, the unexpected methyl trimethoxy cinnamate was obtained exclusively within 3–4 h resulting from alcoholysis reaction, in good yield (99%), which proves that the imide bond is susceptible to hydrolysis.

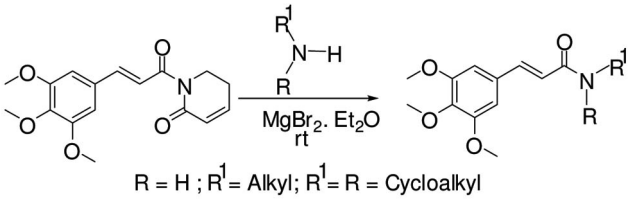
To the best of our knowledge, there are no previous examples of a transamidation reaction between an imide and amine pair. Taking these results into account, the reaction of piplartine **1** and with secondary amines like morpholine, piperidine, pyrrolidine and *N*,*N*-dimethyl amine (entries 5–8) was also studied (Scheme 2). The secondary amines underwent transamidation smoothly providing good yields of the desired products.

We have proposed a plausible mechanism (Scheme 3) following the metal-mediated transamidation[40].

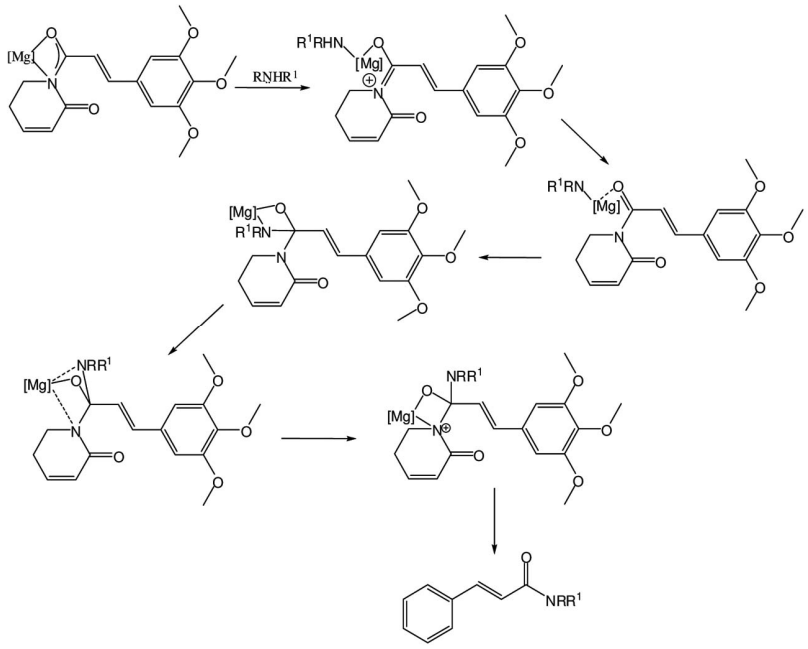
To a stirred solution of piplartine (0.157 mmol) and magnesium bromide etherate (10 mmol%) in acetonitrile (3 ml) at room temperature was added an amine (0.157 mmol). The completion of the reaction was monitored by TLC. After



Scheme 1.



Scheme 2.



Scheme 3. Plausible mechanism for Mg^{II} catalysed transamidation.

Table 2. Optimization of reaction conditions for **1**

Catalyst (mol %)	Solvent	Time (h)	Yield (%)
10	CH_3CN	3	90
10	THF	24	20
10	1,4 dioxane	24	15
10	Toluene	24	5
10	DCM	24	5
10	DMF	24	–
10	DMSO	24	–
10	H_2O	24	–

removing acetonitrile from the reaction mixture, water was added and extracted with ethyl acetate (3 × 20 ml). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated and separated by silica gel chromatography using gradient mixtures of hexane and ethyl acetate as eluents.

In conclusion a simple, efficient and practical method for direct conversion of piplartine to primary or secondary carboxamides carried out by primary as well as secondary amines under mild conditions has been developed. Studies are in progress in order to investigate the scope of this useful transformation.

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Determinants of 'water fleas' (Crustacea: Branchiopoda: Cladocera) diversity across seasonal and environmental gradients of a polluted river

Cladocera (Crustacea: Branchiopoda), commonly known as water fleas, consist of small, primarily freshwater crustaceans, which form a significant component of zooplankton in different aquatic ecosystems[1]. Currently, about 720 species are known across the globe[2], out of which 130 are reported from Indian waters[3]. Although studies are available on the diversity of Cladocera in the riverine systems focusing on their interactions with the environment and subsequent application as bio-indicators of eutrophication[4–7], relatively less information on their ecology is known from the Indian subcontinent.

Some reliable studies[8–10] are available which document the alpha and beta diversity of Cladocera from the floodplain lakes in North East India. However, such reliable studies are not common in