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构建酰胺类化合物的新进展

杨冬兵，马誉志

浙江师范大学化学与材料科学学院，浙江 金华

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摘 要

酰胺键的形成是有机化学中最重要的反应之一。因为酰胺类广泛存在于现代药物和生物活性物质中，然而酰胺键的合成作为当代的挑战经常被忽视。早期合成酰胺的方法有着它们固有的局限性，反应简单快速、方法的普适性越来越受到人们的重视，开发新颖的形成酰胺键的化学方法势在必行。在合成酰胺键的许多方法中，利用催化方法来制备这类重要的官能团备受人们关注，其中金属催化与光催化反应的应用得到广泛关注。催化剂用于形成酰胺键已成为在关键领域中一些最新文献的亮点。醇、醛、羧酸作为底物和有机胺在各种条件下反应得到相应的酰胺。回顾并总结酰胺的合成方法有助于解决目前工艺中存有的问题。

关键词

酰胺，金属催化，光催化，有机胺

New Advances in the Construction of Amide Compounds

Dongbing Yang, Yuzhi Ma

College of Chemistry and Materials Science, Zhejiang Normal University, Jinhua Zhejiang

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Abstract

The formation of amide bonds is one of the most important reactions in organic chemistry. Because amides are widely found in modern pharmaceuticals and bioactives, the synthesis of amide bonds is often overlooked as a contemporary challenge. The early methods of synthesizing amides have their inherent limitations, and the simple and rapid reaction and the universality of the method have attracted more and more attention, and it is imperative to develop novel chemical methods for the formation of amide bonds. Among the many methods for the synthesis of amide bonds, the use

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of catalytic methods to prepare these important functional groups has attracted much attention, among which the application of transition metal catalysis and photocatalytic reaction has received extensive attention. The use of catalysts for the formation of amide bonds has been the highlight of some of the latest literature in key areas. Alcohols, aldehydes, carboxylic acids and organic amines are reacted as substrates to obtain corresponding amides under various conditions. Reviewing and summarizing the synthesis methods of amides can help to solve the problems existing in the current process.

Keywords

Amide, Transition Metal Catalysis, Photocatalysis, Organic Amines

1. 引言

酰胺键作为蛋白质的骨架，不仅在生命中起着至关重要的作用，而且还存在于大量的药理活性化合物和材料中(如尼龙、水凝胶、人造丝、负载型催化剂和用于细胞生长的生物相容性基质)。事实上，在 2006 年的一项调查中[1]，2/3 的候选药物中发现了酰胺键，目前市场上 25%的药物中都存在酰胺键[2]。此外，据估计，“胺酰化”是药物合成中最常用的反应，占比为 16% [3]。

过去制备酰胺的更方便和简单的方法可能是羧酸和胺的直接缩合。然而，众所周知，这种“理想”的酰胺化过程需要非常苛刻的条件(T > 100℃)，以避免形成不反应的羧酸铵盐，从而实现所需的酰胺键的形成(图 1) [4]-[6]。然而，这些程序非常受限，敏感底物(如氨基酸结构片段)与此类高温条件不相容。为了避开酰胺键形成的热条件，酰胺是“传统上”通过在化学计量“偶联”试剂存在下通过羧酸伴侣的预或原位活化(例如，OH 基团转化为更好的离去基团)形成的(图 1) [7]-[13]。这些试剂非常高效，正如肽合成取得了令人难以置信的成功[14]，但该过程通常受到原子经济性不佳的影响。事实上，在 2007 年专门讨论关键绿色化学研究领域的会议上，“酰胺形成避免原子经济性差的试剂”被选为有机化学的首要优先领域[15]。

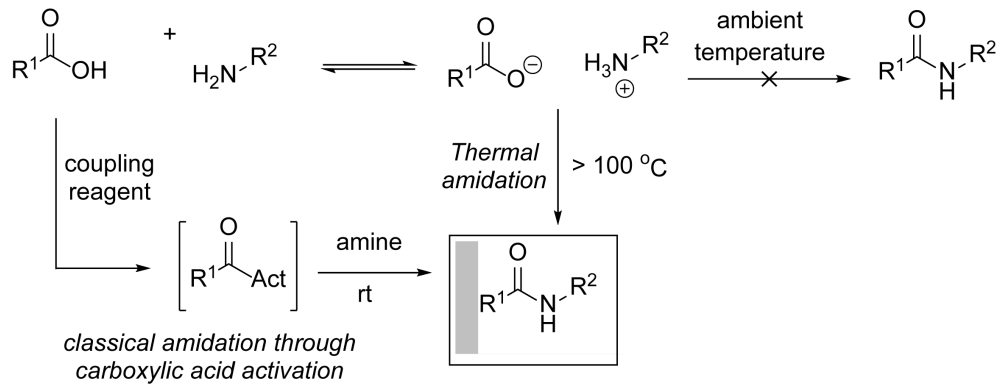

Figure 1. Classic strategies for amide construction
图 1. 酰胺构建的经典策略

近些年来，金属催化[16]-[18]与光催化反应[19]-[22]在分子化学与有机合成领域得到广泛的应用。本综述将介绍通过金属催化与光催化反应来构建酰胺键的合成策略的研究进展，同时为了能够帮助解决现有的合成方法中存在的弊端，本文在综合已发表的文献基础上进行简要地总结和评述。

2. 以醇作为底物合成酰胺

过渡金属催化的酰胺合成直接来自醇和胺，近年来受到了广泛关注(图 2) [23]-[35]。事实上，这种底物在氧化过程中结合在一起，在原子经济性和可持续化学方面非常合适，因为通常只产生氢气作为副产品。

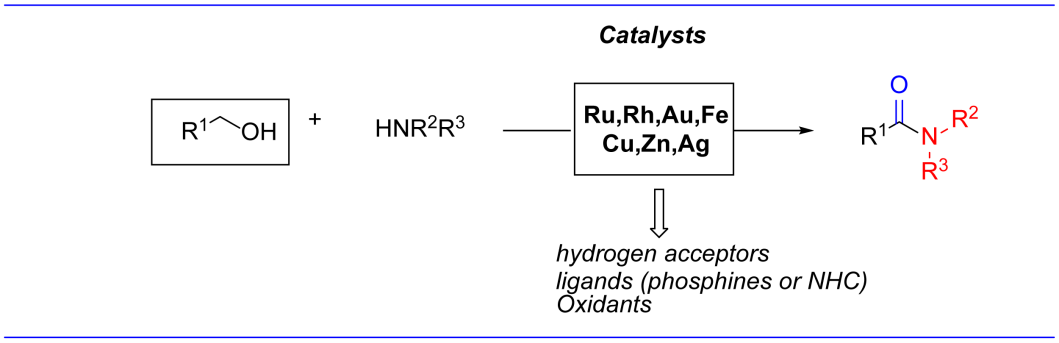

Figure 2. Transition metal-catalyzed amidation of alcohol derivatives
图 2. 过渡金属催化醇衍生物酰胺化

2013 年，Ghosh 小组提出了一种以硝酸铁作为催化剂，仲胺类化合物作为胺源，室温空气氛围下合成酰胺的方法[36]。反应需要经过两个步骤，首先，三价铁类盐与 2,2,6,6-四甲基哌啶－氮－氧化物(TEMPO)形成三价铁金属配位络合物将醇类底物氧化成醛，得到二价铁金属配位络合物，再在氧气的作用下转化为初始状态的三价铁配合物，实现催化剂的循环，完成第一步反应。之后，盐酸胺盐化合物在碱的中和作用下得到仲胺化合物，与醛发生亲核加成得到胺醇化合物。叔丁基过氧化氢(TBHP)作为氧化剂在铁的配合物作用下得到叔丁基氧自由基，攫取胺醇的羟基 α 位碳上的氢原子得到胺醇的自由基中间体，与 TBHP 之间发生单电子转移生成叔丁基氧自由基和叔酰胺目标产物(图 3)。反应所使用的催化剂为硝酸铁，相对廉价易得，且反应仅需在空气当中进行，因此该反应适合应用于大当量的反应，在一些酰胺类化合物工业大规模生产方面有一定的潜在应用价值。但反应底物通常只适用于苄基醇，依赖于芳环的共轭电子效应，底物适用范围存在一定局限性，且反应需要分步进行，实验操作相对繁琐。

2016 年，Shannon S.课题组报道了一种 Cu/ABNO 协同催化体系实现高效的醇和胺类化合物的氧化偶联策略[37]。在该反应中，苄基/脂肪醇和伯胺/仲胺类底物适用于该反应，从而能够广泛获得多种仲酰胺和叔酰胺产物(图 4)。反应表现出优异的官能团相容性，且反应在室温下 30 分钟内完成，体现了反应条件温和和简单快速的优良性。参与反应的氧化剂为纯氧，涉及气体的运输与储存等问题，方法策略的普适性存在一定不足。因此可发展一种金属铜协同催化且在空气条件下进行反应的反应策略，将具有良好的适用性。

2016 年，Hull 等报道一种金属铑催化一锅法烯丙基醇或醛的酰胺化反应[38]。值得注意的是，该反应除了得到醇或醛的酰胺化产物之外意外产生了腈类副产物。反应具体机理如下：化合物烯丙基醇通过碳氢键活化的方式与金属铑催化剂形成过渡态中间体，通过氧化消除得到化合物醛。之后醛与胺类化合物进行亲核加成得到胺醇化合物，与金属铑催化剂之间进行氧化加成或者配体的交换得到与醇氧配位的铑配合物中间体，最终经过 β 氢消除得到酰胺的目标产物(图 5)。而在此过程中得到胺醇化合物后，由于

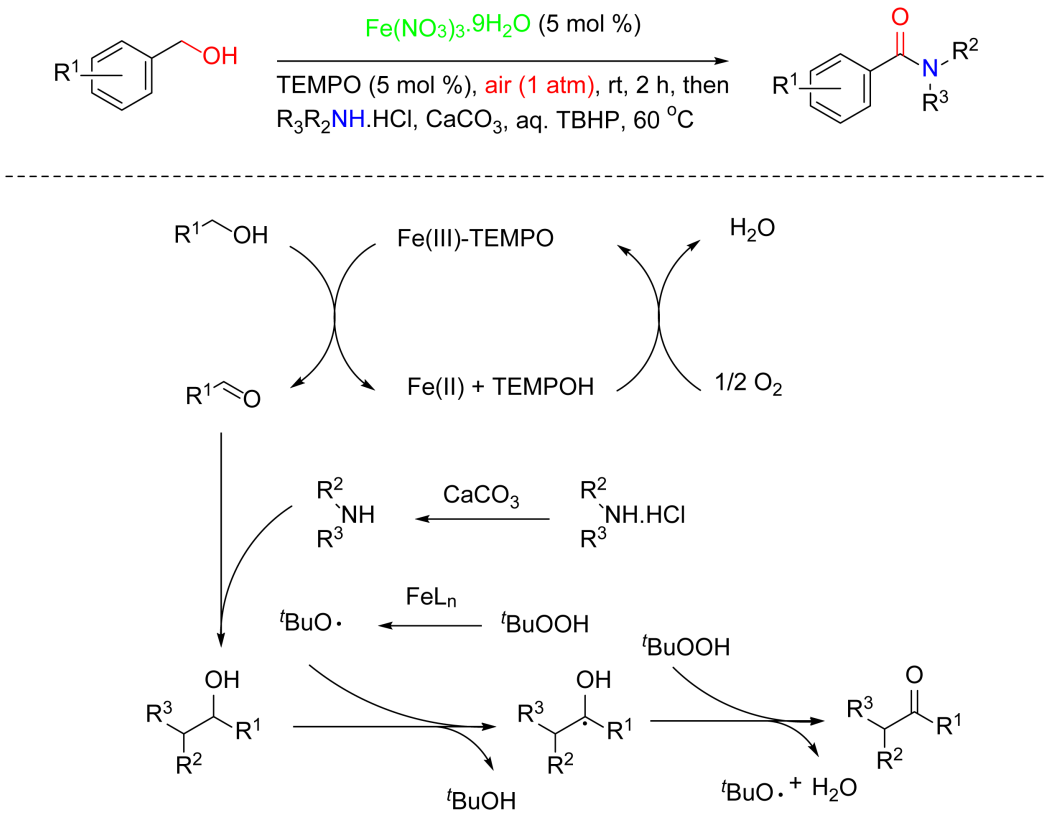

Figure 3. Alcohol as a substrate metal iron catalyzes the construction of amides
图 3. 醇为底物金属铁催化构建酰胺

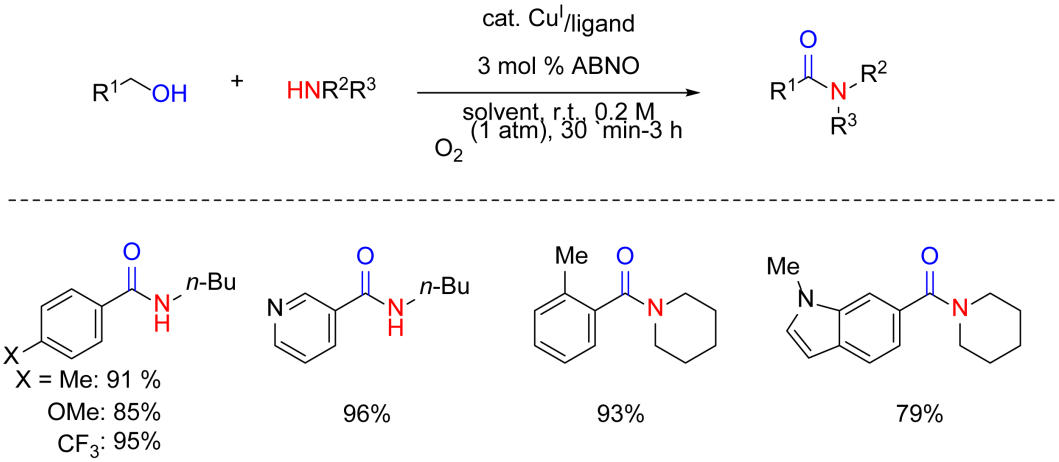

Figure 4. Alcohol as a substrate metal copper catalyzes the construction of amides
图 4. 醇为底物金属铜催化构建酰胺

仲醇的不稳定性有可能会进行醇的消除反应脱水生成腈类化合物或者烯基胺类化合物，这是副产物产生的主要原因。反应通过金属的催化进行反应，可适用于醇与醛内底物，反应兼容性优良，且一锅法避免了分步反应的操作繁琐与产率损失等问题，具有良好的化学经济性。但金属铑催化剂的价值成本高，不适用应用于大当量的反应与工业生产。因此，可发展一种廉价金属参与催化的一锅法反应策略，且具有良好的底物适用范围。

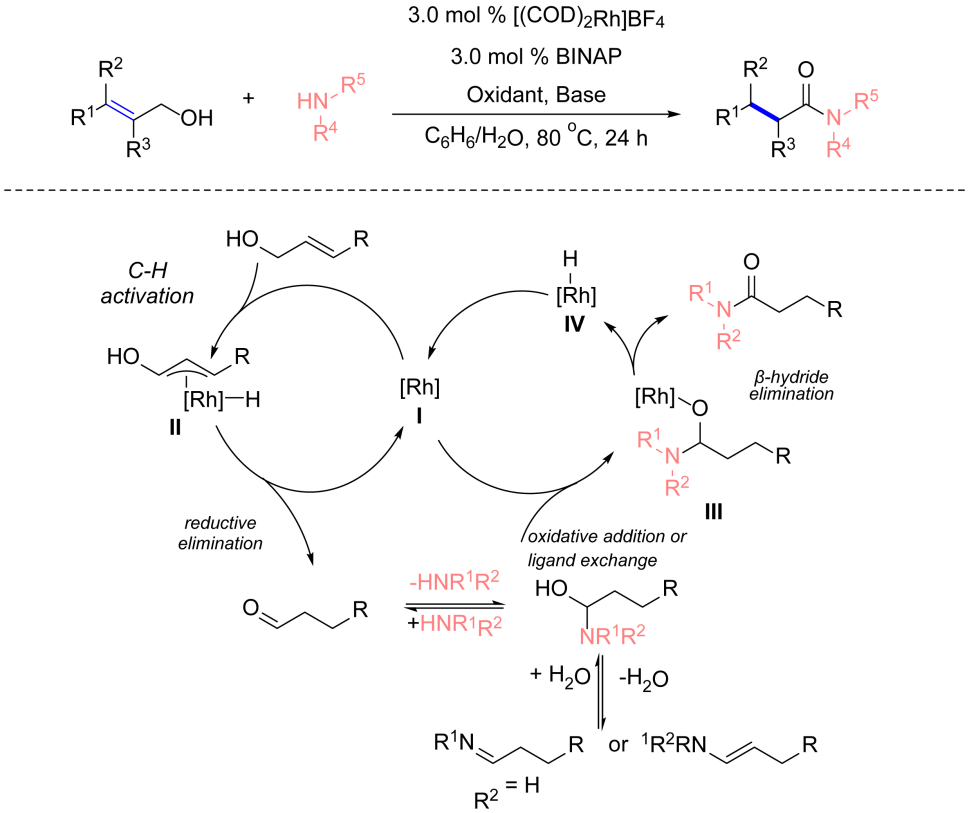

Figure 5. Alcohol as a substrate for metal rhodium-catalyzed amide construction
图 5. 醇为底物金属铑催化构建酰胺

3. 以醛作为底物合成酰胺

过去几十年中，醛类作为直接酰胺化过程的底物的使用也得到了广泛研究(图 6) [39]-[58]。

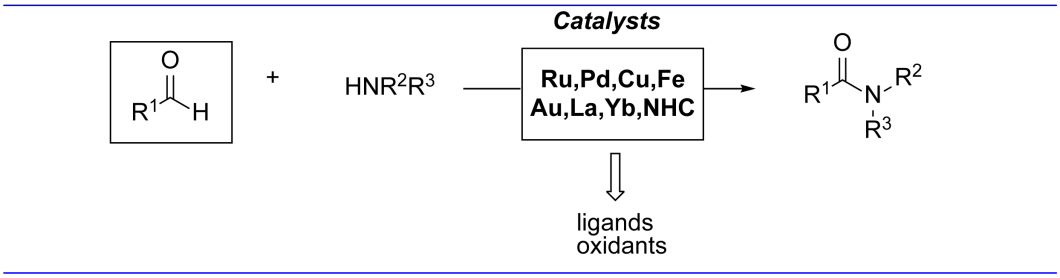

Figure 6. Oxidative amidation of aldehydes
图 6. 醛的氧化酰胺化

2014 年，Dasheng Leow 课题组报道了一种无过渡金属参与的可见光诱导的芳醛酰胺化反应。光催化剂吩嗪乙硫酸盐，反应在环境温度下进行，并使用空气作为唯一的氧化剂。反应条件温和，无过渡金属参与以及反应组分简单，为酰胺键的形成提供了一种经济、绿色和温和的构建策略[59]。反应首先是由吩嗪乙硫酸盐在光照条件下达到激发态，与仲胺化合物之间发生单电子转移得到叔胺阳离子自由基中间体，在碱性条件会发生不均衡的双键的还原得到苯并环化合物。之后在空气条件下被氧化成基态的光敏剂吩嗪乙硫酸盐实现催化体系的循环，以及得到 H_2O_2。最终通过 H_2O_2 去氧化胺醇得到酰胺的目标产物(图 7)。

反应无过渡金属参与，使用有机化合物催化剂体现了反应的绿色与环保性，符合绿色化学原则。但反应底物通常为芳醛，而脂肪族类底物并不能在该反应中得到一定的兼容，底物适用性存在一定的限制。开发一种适用于脂肪醛的绿色经济的酰胺化反应策略具有一定研究价值。

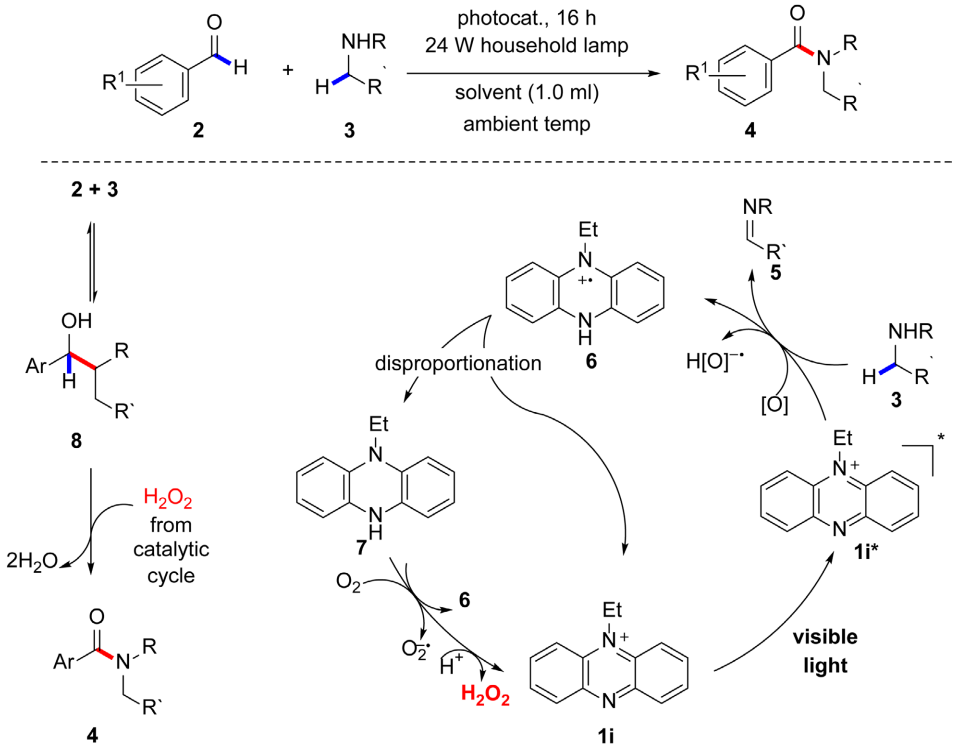

Figure 7. Aldehyde as substrate phenozine acesulfate as photosensitizer photocatalytic building amide
图 7. 醛为底物吩嗪乙硫酸盐为光敏剂光催化构建酰胺

2023 年，夏吾炯课题组利用可见光介导的配体－金属电荷转移(LMCT)过程下实现醛与胺之间的直接脱氢酰胺反应[60]。该合成策略对脂肪族和芳香族组分具有良好的官能团耐受性和广泛的底物范围。反应主要是通过 LMCT 策略产生氯原子，通过氯原子去攫取醛上的氢原子得到酰基自由基，氯原子再与酰基自由基进行偶联得到酰氯。同时部分酰氯与氟化钾反应被转化为酰氟，最终与仲胺之间发生亲核加成得到酰胺产物(图 8)。反应的底物适用范围较广，芳醛与脂肪醛均能在该反应策略中得到良好的兼容，且氯化铁与氯化亚铁均是相对廉价易得的催化剂，经济性良好。但反应需要通过光介导催化反应，存在一定的反应适用限制。相对来讲，无需光介导的金属催化的反应策略适用范围更广，可具有一定的工业应用前景。无光介导的廉价金属催化剂参与反应，且底物适用范围较广的反应策略具有一定的研究意义。

2024 年，Arindam Indra 课题组发展了一种 $CsPbBr_3$ 作为光催化剂，二价镍化合物作为协同催化剂通过交叉偶联的策略构建酰胺键与一系列酰胺化合物[61]。反应过程是光敏剂 $CsPbBr_3$ 在光照条件下达到激发态的$[CsPbBr_3]^*$，与仲胺化合物之间发生单电子转移，得到仲胺阳离子自由基与$[CsPbBr_3]^-$。$[CsPbBr_3]^-$与作为协同催化剂的 $Ni^{II}(dmgH)_2$(dmgH = dimethyl glyoximato)发生单电子转移得到基态的 $CsPbBr_3$ 完成光催化剂的循环，同时生成一价镍配合物。一价镍配合物与 O_2 之间发生单电子转移得到过氧自由基阴离子，过氧自由基阴离子攫取芳基甲醛上的氢质子得到过氧自由基与芳基羰基负离子。之后羰基负离子经过光氧化系统中被氧化成芳基酰基自由基。芳基酰基自由基与仲胺阳离子自由基之间进行自由基偶联得到芳基甲酰胺阳离子，通过过氧自由基攫取氮上的氢原子得到酰胺阳离子自由基与过氧化氢，最终酰胺

阳离子自由基经过单电子还原得到酰胺的目标产物(图 9)。这种光与金属配合物协同催化自由基交叉偶联策略简单高效，底物适用范围相对较广。但金属铅与镍类催化剂相对价格高昂，反应成本较高。

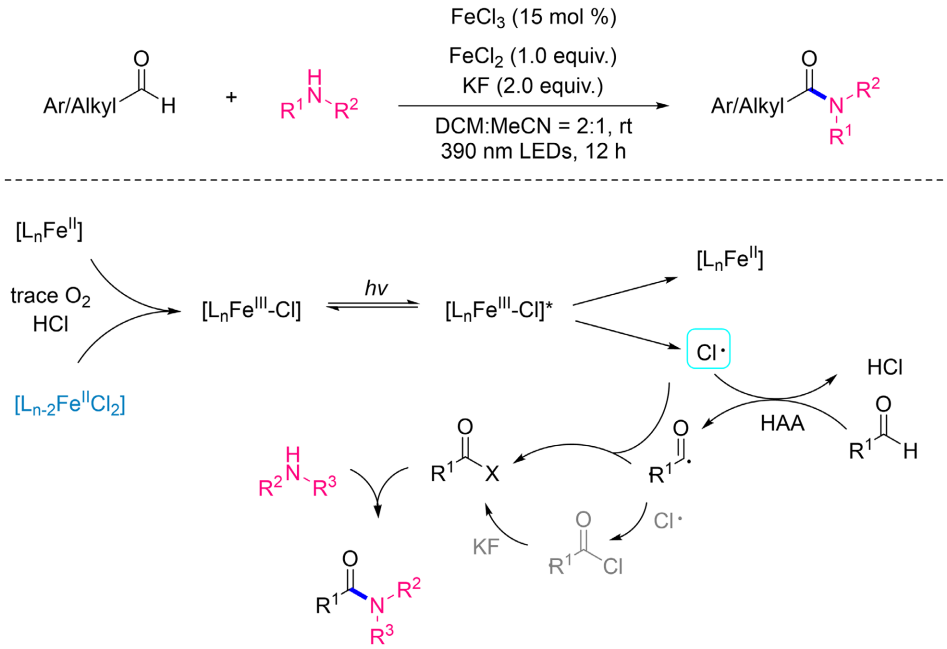

Figure 8. Aldehydes as substrates for light-mediated LMCT strategy to construct amides
图 8. 醛为底物光介导的 LMCT 策略构建酰胺

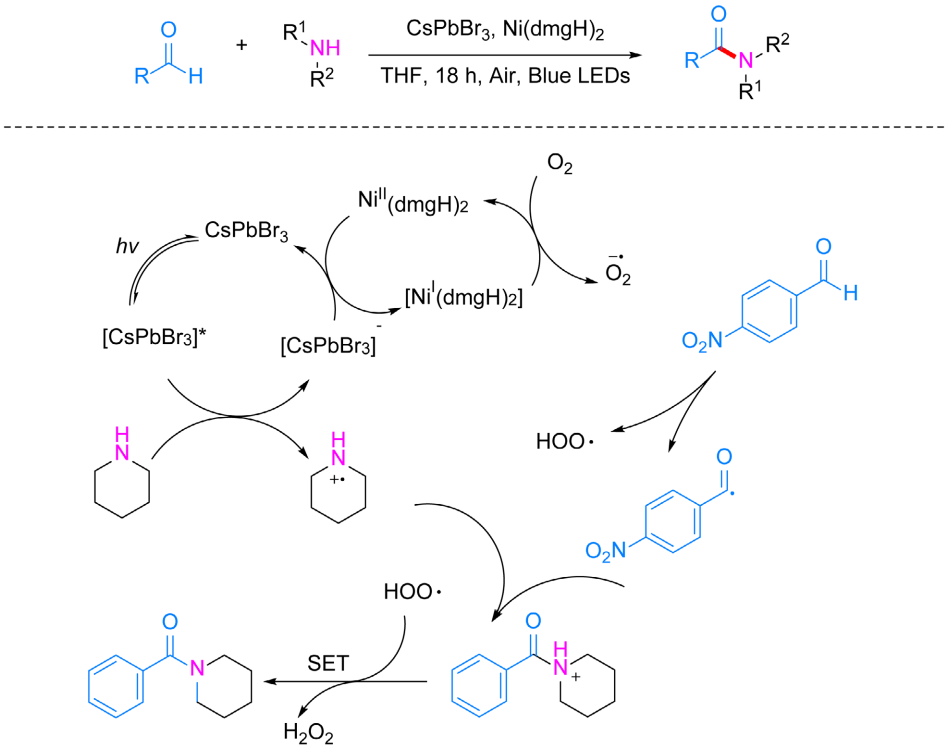

Figure 9. Aldehyde is the co-catalytic construction of an amide by the substrate $CsPbBr_3$ and nickel metal
图 9. 醛为底物 $CsPbBr_3$ 与金属镍协同催化构建酰胺

4. 以羧酸为底物合成酰胺

伯烷基硼酸，如烷基或芳基硼酸，是 α-羟基羧酸脱水缩合酰胺化的高活性催化剂[62]-[64]。因此过去以羧酸为底物合成酰胺往往无金属催化剂参与反应。例如 2013 年，Kazuaki Ishihara 课题组发展了一种甲基硼酸作为催化剂，苯甲酸辅助催化芳 α-羟基羧酸与伯、仲胺缩合构建 α-羟基酰胺类化合物的策略[65]。同时，无羟基取代的芳烷基羧酸也适用该反应。反应主要是利用甲基硼酸与 α-羟基羧酸或芳烷基羧酸底物之间形成环化过渡态中间体，经过与氨烷基胺基阳离子之间发生亲核取代反应脱去水与甲基硼酸得到酰胺目标产物(图 10)。以硼酸为反应催化剂，无过渡金属参与反应符合绿色化学原则。但反应通常需要高温下进行，反应条件相对苛刻。可进一步发展一种无过渡金属参与反应，且条件温和，反应可在室温条件进行的反应策略。

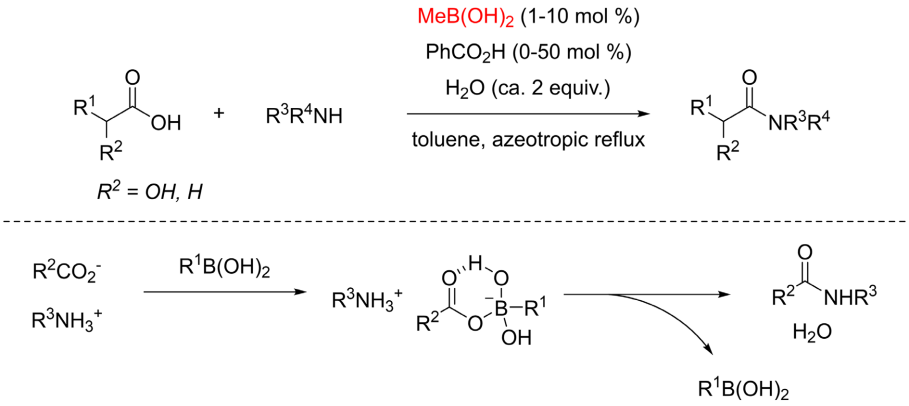

Figure 10. Early carboxylic acids were used as substrates to construct amides catalyzed by boric acid, a non-metallic catalyst
图 10. 早期羧酸为底物以非金属催化剂硼酸催化构建酰胺

而近些年，金属催化与光催化反应逐渐被应用于羧酸为底物合成酰胺的反应当中。2017 年，Alex M. Szpilman 报道了利用胺和四氯化碳之间发生电荷转移形成络合物，作为激活胺进行光化学反应构建酰胺类化合物的新策略[66]。该原理在原料羧酸和胺形成温和、无过渡金属、可见光辅助的脱烷基酰胺中过程中得到证明。反应首先是在胺和四氯化碳之间发生电荷转移形成络合物后，经过可见光诱导脱去氯化氢和三氯甲烷后得到亚胺阳离子，羧酸脱氢质子形成羧基负离子之后，氧负电子对进攻亚胺的碳氮双键形成叔胺化合物。随后叔胺氮与原料仲胺氮上的孤对电子同时进攻羰基碳，形成分子内环化和分子间中间体，经过中间体的重排得到酰胺目标产物(图 11)。但反应涉及有毒溶剂四氯化碳的应用，不符合环境友好与绿色化学原则。因此，可进一步发展绿色溶剂参与反应的策略。

2021 年，Alex M. Szpilman 课题组报道了一种太阳光辅助的肽偶联反应策略，它在机制上依赖于 4-二甲基氨基吡啶－烷基卤化物电荷转移复合物的太阳光活化，以原位生成新型偶联试剂。所得的偶联方法快速，不需要干燥溶剂或惰性气氛，并且与所有最常见的氨基酸和保护基团兼容[67]。肽偶联可以在克级反应中得到良好应用，无需优化条件。反应通过 4-二甲氨基吡啶(DMAP)与一溴三氯甲烷形成电荷转移络合物，在光照条件达到三重激发态，经过脱去三氯甲烷得到芳基亚胺阳离子，4-二甲氨基吡啶对亚胺阳离子的碳氮双键进行亲核加成得到吡啶氮阳离子中间体。随后与羧酸之间脱去吡啶配合物得到酯氧偶联产物，最终通过 DMAP 催化剂的作用下与胺原料发生亲核加成后得到肽类化合物(图 12)。

2020 年，Patricia Marcé 课题组发展了一种从羧酸直接合成伯酰胺和仲酰胺的新策略[68]。使用硝酸镁或咪唑作为低成本且容易获得的催化剂，尿素作为稳定且易得的氮源。该方法对于伯酰胺和甲酰胺的直接合成有着高效的适用性，避免了使用氨和甲胺气体，因为氨和甲胺气体的保存与使用可能很繁琐。

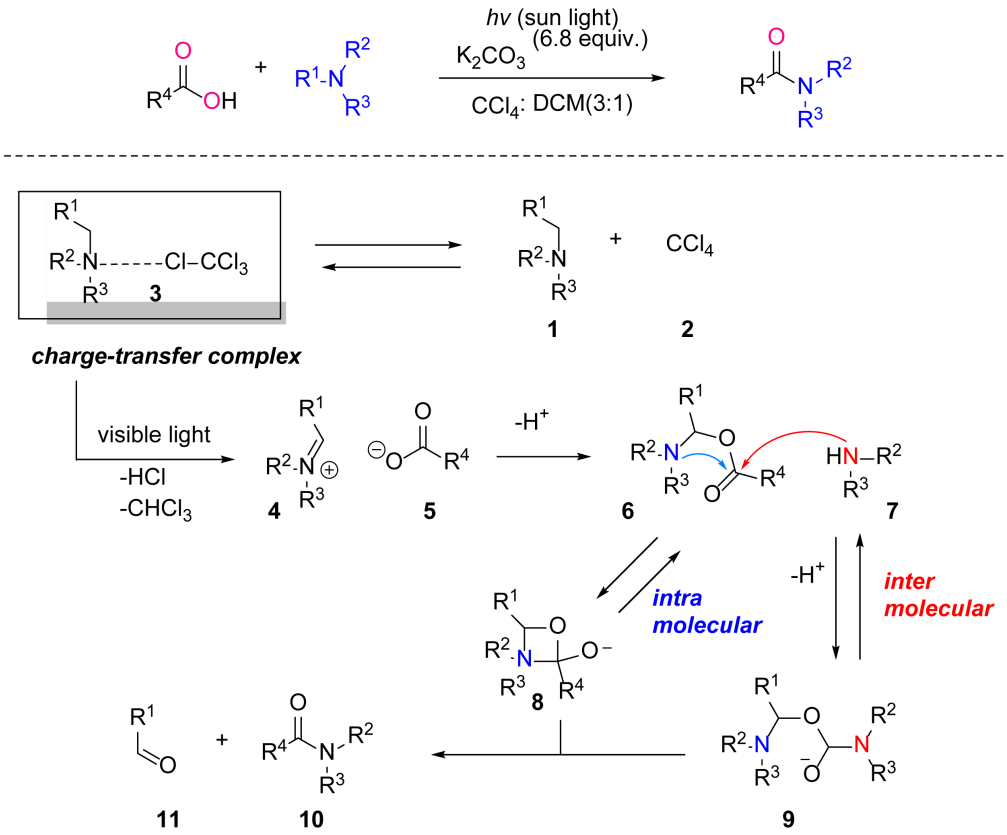

Figure 11. Carboxylic acids as substrates light-mediate the formation of amine complexes to catalyze the construction of amides

图 11. 羧酸为底物光介导胺络合物的形成催化构建酰胺

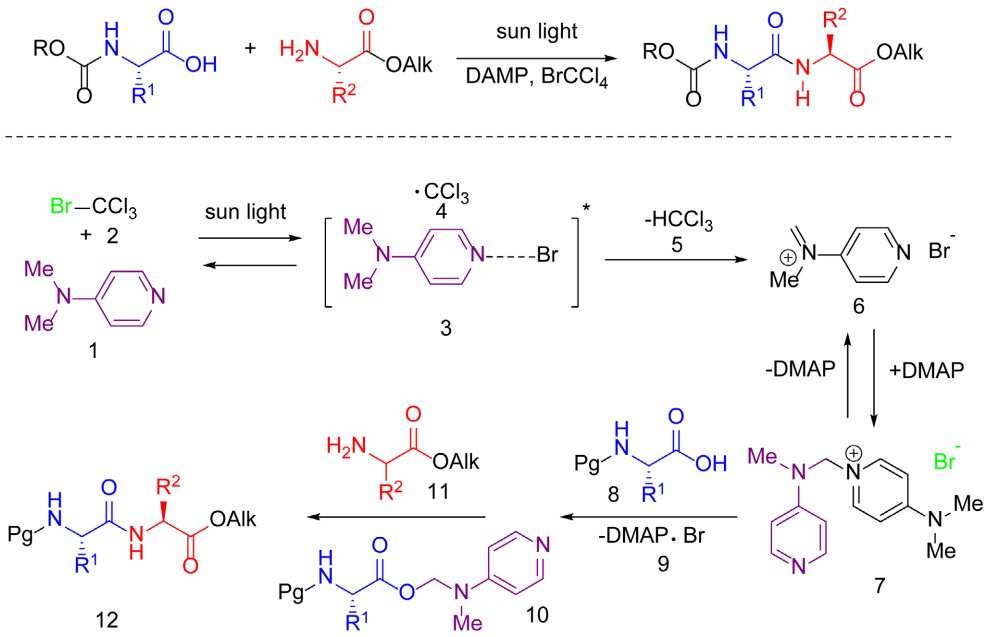

Figure 12. Carboxylic acids as substrates light-mediate the formation of pyridine complexes to catalyze the construction of amides

图 12. 羧酸为底物光介导吡啶络合物的形成催化构建酰胺

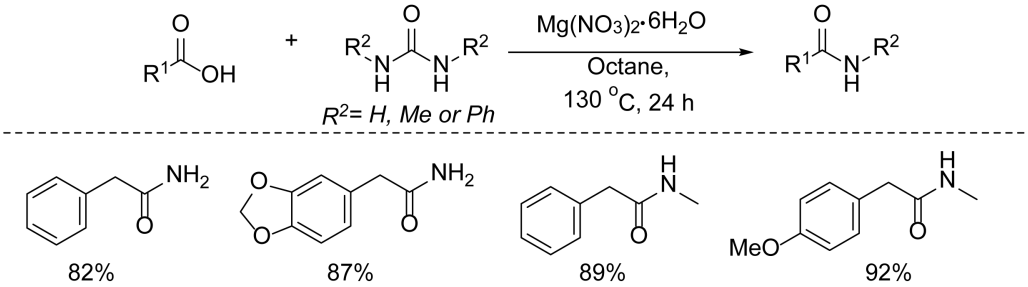

Figure 13. Carboxylic acids as substrates, magnesium metals, catalyze the construction of amides
图 13. 羧酸为底物金属镁催化构建酰胺

此外，转化不需要使用通常需要的偶联剂或活化剂(图 13)。反应的底物通常为芳基羧酸，相对底物适用范围存在一定局限性，且反应需要在高温条件下进行，反应条件相对复杂。

5. 总结与展望

目前，用于酰胺合成的过渡金属催化与光催化方法，对于合成含酰胺键的化合物有着直接的影响.这些反应不仅对环境友好，也可以将成本降到最低，反应简单快速，底物适用范围广。这些方法最初都是应用在合成小分子上，但是原理和机理都可以扩展应用到合成肽类结构上，尤其适用于那些含有非天然的氨基酸片段的肽类结构的合成。催化方法的高效以及固有的选择性都会给对映选择和化学选择的反应提供新的机会，金属催化与光催化反应将进一步的被广泛应用于酰胺与酰胺衍生物的合成当中。未来将发展更多更具有选择性、高效性、绿色环保的催化体系，应用于酰胺的构建当中。科研工作者将可能利用以下方式去发展更优良的反应策略：选用廉价易得的金属或有机催化剂去替换贵重金属催化剂来降低反应成本，且适用于反应的高效催化剂提升反应效率，发展室温反应控制反应条件的温和，适用于不同类底物例如脂肪族与芳环类底物均适用的反应策略，选用绿色溶剂与反应组分等。而这些方法策略为多种含酰胺结构单元的天然产物、药物分子和生物活性分子的合成、修饰和改性提供新的选择和路径，有望在有机合成、药物开发和高分子材料等领域得到广泛的应用。

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