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Progress in Lewis Acid Catalyzed Aryl C-Glycosylation

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Abstract

Aryl C-glycosides, as inhibitors of glycosyltransferases and glycosidases, act as regulators in a range of biological processes. The drugs based on the aryl C-glycosides for the therapy of various diseases have also been successfully developed. Due to its excellent biological and chemical properties, the synthesis of aryl C-glycosides in the past few decades has attracted the attention of many biologists and chemists and has become a rapidly growing research field. However, there are always some difficulties in the synthesis of aryl C-glycoside compounds. Based on the studies of aryl C-glycoside compounds by domestic and foreign scholars, this paper summarizes the research progress on the Lewis acid-catalyzed aryl C-glycosylation, and discusses the classification of synthetic methods. This review covers the literature from 1983 to 2017 and provides references and help for relevant researchers.

Keywords

Catalyst, Aryl C-Glycosylation, Lewis Acid

路易斯酸催化的芳基C-糖苷化研究进展

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摘　要

芳基C-糖苷类化合物作为糖基转移酶和糖苷酶的抑制剂，在一系列生物过程也作为调节剂，针对各种疾

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病，应用芳基C-糖苷类化合物所研发的药物也得到成功的开发，由于它优异的生物与化学性质，在过去几十年中合成芳基C-糖苷类化合物，已经引起了众多生物学家与化学家的关注，成为快速发展的领域。一直以来，芳基C-糖苷化合物都存在合成困难的问题，本文基于国内外学者对芳基C-糖苷类化合物的研究，总结了由路易斯酸催化的芳基C-糖苷化的研究进展，并且进行了类别讨论，涵盖了1983年至2017年的文献。希望本文可以为相关研究工作者提供参考与帮助。

关键词

催化，芳基C-糖苷化，路易斯酸

1. 介绍

糖苷是糖的半缩醛羟基与配基缩合，失去一份子水而形成的一类具有广泛生理活性的化合物，也是糖在自然界中存在的主要形式。糖类化合物具有多种生物学活性，在生命过程中发挥着极其重要的作用，其合成也越来越受到人们的重视。C-糖苷是一类具有碳水化合物单元的化合物，其通过 C-C 键与糖苷配基或另一碳水化合物单元连接。近年来，C-糖苷化已经被很好地开发以改善立体选择性，并已广泛用于化合物的合成[1] [2] [3]。图 1 中列出了自 1990 年以来合成的代表性天然 C-糖苷类化合物。它们包括 aspalathin [4]，葛根素[5]，芒果苷[6]，Chafuroside A [7]，Ravidomycin [8]。与 O-和 N-糖苷化相比，C-糖苷化具有高产率和特定立体选择性的优势，但是多种 C-糖苷类天然产物存在提取困难，来源少等问题，使得 C-糖基化发展更加缓慢。糖基供体对于糖苷化反应的立体选择性还有产率都有着显著的影响，基于糖基供体对于 C-糖苷化反应进行分类包括糖内酯，糖基卤化物，乙二醇，酰亚胺/磷酸酯和甲基糖苷，乙酸糖基酯，1,2-脱水糖，硒代糖苷/碲代糖苷，硫代糖苷/亚砜/砜[9] [10]。传统的芳基 C-糖基化反应通常涉及金属试剂(例如锡，锌，锂，铝和格氏试剂)与糖基供体的亲核反应。由于金属试剂的空气和水分敏感性，这些反应效率很高但不易处理。在过去的十年中，人们已经做出了很多努力来开发更温和、更有效和高度立体选择的方法。涉及的促进剂有路易斯酸，包括 TMSOTf，$BF_3{\cdot}OEt_2$，$SnCl_4$，HBF_4 和 $Sc(OTf)_3$ 等。这些反应对于 C-糖苷类天然产物的合成具有指导意义。本文综述了过去四十年中由路易斯酸作为促进剂催化的芳基 C-糖基化反应的研究进展。

2. 路易斯酸催化的芳基 C-糖苷化

2.1. 通过 TMSOTf 催化的芳基 C-糖苷化

在很多年前就已经开发了包括 O-糖基化和随后的原位 O→C 重排的弗里斯型糖基化。该方法应用于合成具有许多生物活性的芳基 C-糖苷，如糖基类黄酮[11]，包括 Chaufurosides A 和 B [12]、Mangiferin [6]、Aspalathin。通过 TMSOTf 催化的芳基 C-糖苷化，产率有的只有 12%，有的也可达到 82%。Chaufurosides A 和 B 的合成始于四-O-苄基-D-葡糖基亚氨酸酯 1 和苯乙酮衍生物 2 之间的糖基化。通过 TMSOTf 催化的 Fries 重排获得 β-异头物形式的芳基 C-糖苷 3，产率为 74% (图 2)。

2.2. 通过 $BF_3{\cdot}OEt_2$ 催化的芳基 C-糖苷化

$BF_3{\cdot}OEt_2$ 催化的芳基 C-糖苷化，糖基供体包括糖内酯、过氧苄基葡糖基 α-氟化物、2,3,4,6-四-O-苄

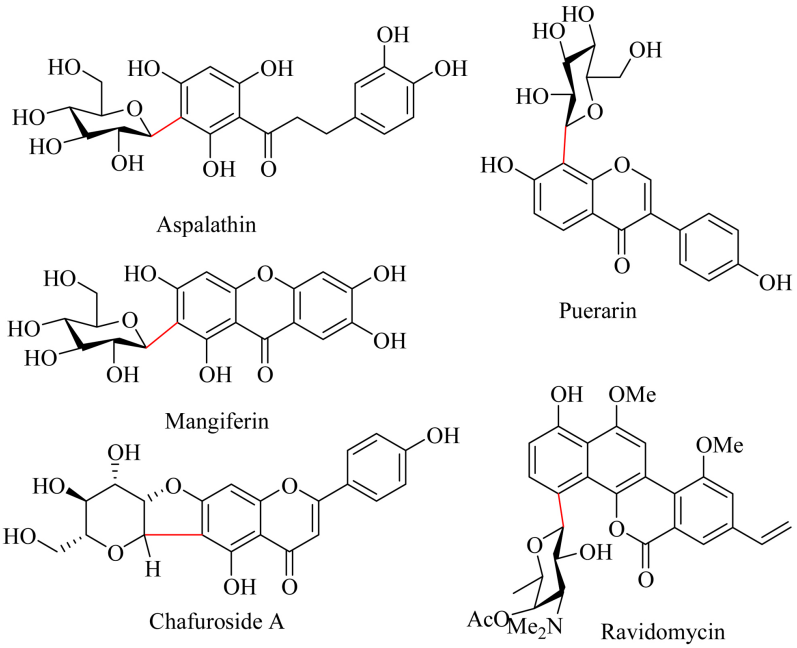

Figure 1. Representative natural C-glycoside compounds
图 1. 代表性天然 C-糖苷类化合物

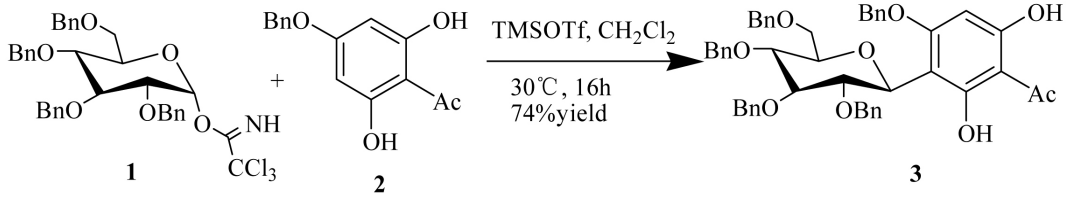

Figure 2. Aryl C-glycosylation catalyzed by TMSOTf
图 2. TMSOTf 催化的芳基 C-糖苷化

基-α-D-吡喃葡萄糖、甲基葡糖苷、四-O-甲基吡喃葡萄糖等，产率达到 60%至 96%不等[13]-[19]。Aspalathin 是一种二氢查尔酮 C-糖苷，具有抗氧化和抗突变作用。皂苷，即 6-C 和 7-O-二-β-D-吡喃葡萄糖基-4',5,7-三羟基黄酮，具有抗氧化，降血糖和血液保护活性。佐藤小组报道了应用 $BF_3{\cdot}OEt_2$ 促进的芳基 C-糖基化，完成了皂苷和 aspalathin 的合成[4] [20]。过氧苄基葡糖基 α-氟化物 4 与 2,4-O-二苄基氯苯乙酮 5 在二氯甲烷体系中通过 $BF_3{\cdot}OEt_2$ 催化得到所需 β-葡萄糖苷 6，产率 96% (图 3) [13]。

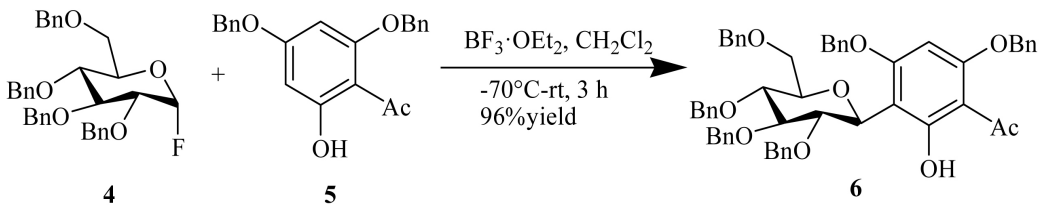

Figure 3. Aryl C-glycosylation catalyzed by $BF_3{\cdot}OEt_2$
图 3. $BF_3{\cdot}OEt_2$ 催化的芳基 C-糖苷化

该 C-糖基化也通过在 TMSOTf 存在下用过-O-苯基葡糖基-α-三氯亚氨酸酯处理 2,4-O-二苄基氯苯乙酮 5 来实现，产率略低，只有 79%。

2.3. 通过 $Sc(OTf)_3$ 催化的芳基 C-糖苷化

已报道，直接使用未受保护的糖乳醇与 C-亲核试剂偶联代表了一种有吸引力的方法，可用于芳基 C-糖苷化[21] [22] [23] [24]。其他类型的未受保护的糖醇如 2-乙酰氨基糖，庚糖，木糖和半乳糖与 C-亲核试剂如 1,3-二羰基化合物和 1,3-恶嗪-2-硫酮，在碱($NaHCO_3$，Na_2CO_3，NaH 或 KOH)或路易斯酸($InCl_3$，$CoCl_2$，$Sc(OTf)_3$)存在下反应，得到相应的 C-吡喃-或 C-呋喃糖苷类，具有高 β-立体选择性的良好收率[25] [26] [27] [28] [29]。作为 $Sc(OTf)_3$ 促进未保护的糖内酯与芳基化合物的 C-糖基化的实例，葡萄糖 7 与 8 的直接糖基化产生 β-C-芳基糖苷 9，产率 65% (图 4) [30] [31] [32] [33] [34]。

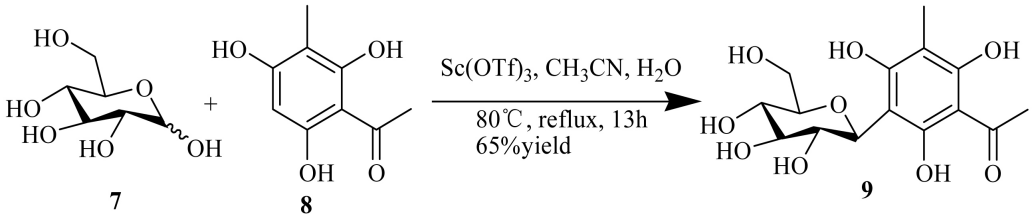

Figure 4. Aryl C-glycosylation catalyzed by $Sc(OTf)_3$
图 4. $Sc(OTf)_3$ 催化的芳基 C-糖苷化

2.4. 通过 $SnCl_4$ 催化的芳基 C-糖苷化

形成 C-糖苷键的一般方法基于在糖基供体的亲电子中心上添加亲核碳。最广泛使用的糖基供体分为四个主要组(良好的离去基团，糖内酯，甘氨酸和 1,2 个脱水糖)用作亲电子供体当与有机铜酸盐，有机锡，有机锌，氰化物，烯丙基格氏试剂，乙烯基甲硅烷基试剂和活性芳香族化合物等反应时以产生 C-糖苷键[35]。通过 $SnCl_4$ 催化的芳基 C-糖苷化，糖基供体有乙酸糖基酯、1-O-甲基糖等，产率在 60%至 76%之间[36] [37] [38] [39]。与 O-糖基卤化物的 C-糖基化相似，1-O-甲基糖类通过氧代羰基离子与 C-亲核试剂进行有效的亲电子 C-糖基化需要强烈的酸性条件[35] [40] [41] [42] [43] [44]，在 $SnCl_4$/AgOTf 的存在下，甲基葡糖苷 10 与 1,4-二甲氧基萘 11 的反应顺利进行，得到 β-C-芳基-葡萄糖苷 12，产率为 76% (图 5) [45] [46] [47] [48]。

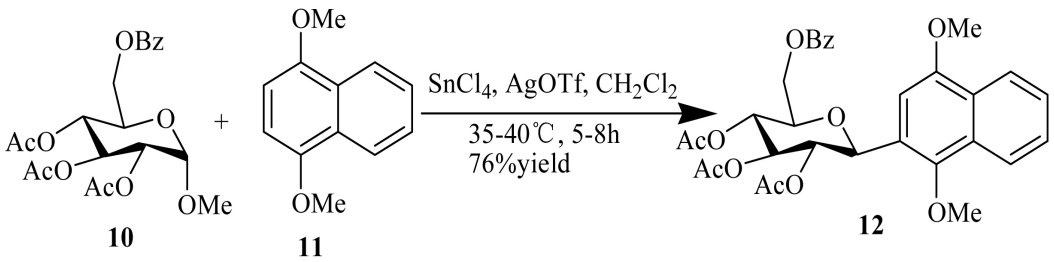

Figure 5. Aryl C-glycosylation catalyzed by $SnCl_4$
图 5. $SnCl_4$ 催化的芳基 C-糖苷化

2.5. 通过 HBF_4 催化的芳基 C-糖苷化

在一些由路易斯酸催化的芳基 C-糖苷化反应中，使用较强的路易斯酸并不能获得所需产物，但是用 HBF4 水溶液便可成功促进反应。例如从海洋链霉菌相关放线菌中分离的 Marmycin A 显示出各种生物活性，包括抗菌，抗肿瘤，酶抑制和细胞抑制作用[49]。Marmycin 具有独特的六环结构，其由连接糖对应物和芳族苯并[α]蒽醌的 C-和 N-糖苷键组成。将 14 连接到糖部分 13 上，并通过铜介导的乌尔曼胺化，得到化合物 15，产率为 81%。接下来尝试使用常用的强路易斯酸不能提供所需的产品，但 HBF_4 水溶液

成功地促进了 C-糖基化，并且 Marmycin A 以 13%的产率得到(图 6) [50] [51]。

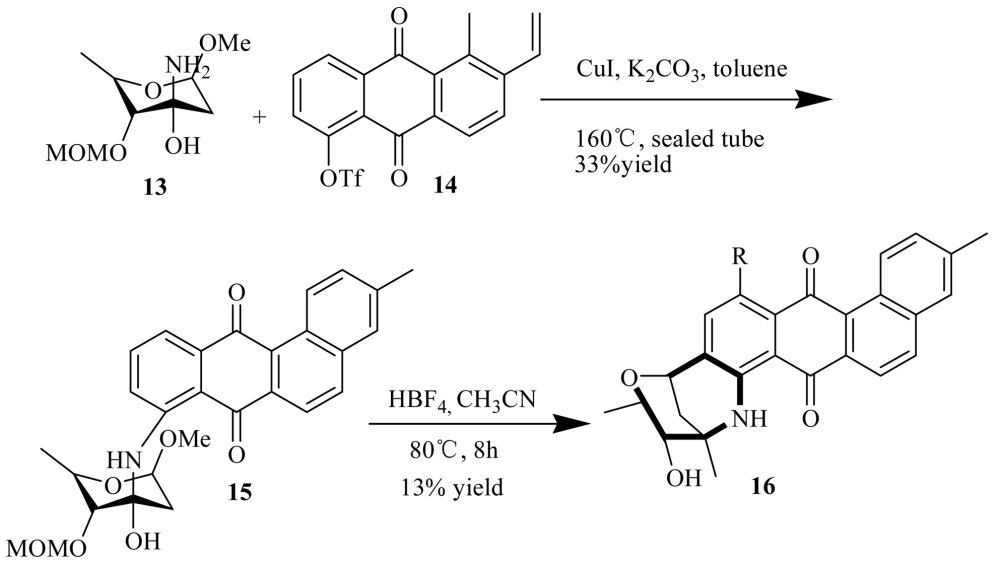

Figure 6. Aryl C-glycosylation catalyzed by HBF_4
图 6. HBF_4 催化的芳基 C-糖苷化

3. 总结

作为全合成中广泛使用的方法，芳基 C-糖苷化在过去几十年中已成为快速发展的领域，方法涉及糖基阳离子、阴离子、自由基物质和衍生自一系列糖前体的过渡金属络合物，重排和环化也为芳基 C-糖苷化提供了替代途径。在芳基 C-糖苷化的发展中，由路易斯酸(TMSOTf，$BF_3{\cdot}OEt_2$，$SnCl_4$，HBF_4 和 $Sc(OTf)_3$)所催化的反应，更温和有效且具有高度立体选择性，使之具有重要意义。在大多数情况下，立体选择性是底物控制的，但是立体选择性芳基 C-糖基化反应的确切机制和基本原理仍未完全了解。许多芳基 C-糖基化反应中仍存在使用的条件苛刻和制备糖前体(例如 1,2-脱水糖)困难等问题。在这个快速发展的领域中，尽管取得了相当大的进展，但是为了确定控制芳基 C-糖基化的立体选择性的基本规则，仍需要不断努力，并且积极寻求高效控制天然产物合成的区域选择性和立体选择性芳基 C-糖基化的一般方法，以合成各种结构复杂且具有生物学意义的芳基 C-糖苷。

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