

连续微反应加氢技术在有机合成中的研究进展

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摘要: 加氢反应是有机合成中很常见的一种反应类型, 采用常规的间歇加氢釜具有反应效率低、操作烦琐和安全性差等问题。而连续加氢微反应器进行非均相催化加氢反应能提供更高的传质性能, 催化剂的回收利用与产物的纯化也更为方便, 能极大地提高生产效率, 减少贵金属催化剂的损失。因为这些优点, 连续微反应加氢技术得到了越来越多的关注。本文阐述了连续微反应加氢技术中常用的微反应器与固体金属催化剂类型, 以及不同官能团非均相高效催化加氢的研究进展, 在此基础上, 对该技术在精细化工领域的应用进行了展望。连续微反应加氢技术使得加氢过程可以在更安全、更高效、更环保的条件下完成, 具有很高的工业应用价值, 是未来化学化工领域重点发展的方向之一。

关键词: 连续流; 催化加氢; 微反应器; 选择性加氢; 非均相反应

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Research progress of continuous hydrogenation in organic synthesis

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Abstract: The hydrogenation reaction is a type of reaction which is very common in organic synthesis. The conventional batch hydrogenation reactor has the problems of low reaction efficiency, cumbersome operation and poor safety. The method of heterogeneous hydrogenation in a continuous microreactor can provide higher mass transfer performance, easy recycling of the catalyst and the purification of the product are more convenient, which can greatly improve the production efficiency and reduce the loss of precious metal catalysts. With these advantages, continuous hydrogenation technology in microreactors has received more and more attention. The research progress of commonly used microreactors and solid metal catalyst types, as well as heterogeneous high-efficiency catalytic hydrogenation of different functional groups in continuous microreactor are described in this paper. On this basis, the application of this technology in the field of fine chemicals is prospected. The continuous microreactor technology enables the hydrogenation process under safer, more efficient and more environmentally friendly conditions. It has high industrial application value and is one of the key development directions in the chemical industry in the future.

Key words: continuous flow; catalytic hydrogenation; microreactor; selective hydrogenation; heterogeneous reaction

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引 言

还原反应是化学合成中一个重要的反应,约有1/4的化学化工合成路线中包含至少一次的还原过程^[1]。在还原反应中,均相过程往往通过 LiAlH_4 与 NaBH_4 等强还原剂^[2-3]或硼烷试剂^[4]实现原料的快速还原,这种方法具有还原效率高、过程简单等优点,然而这种方法存在着原料成本高以及产生大量废液等问题。另外最常见的还原反应过程为非均相催化加氢过程,该方法通常在贵金属(钯、铂、钌和铑等)固体催化剂催化下,实现氢气与底物的加氢反应,该方法具有很好的原子经济性,并且可以回收催化剂,降低过程成本^[5]。这类非均相催化加氢反应过程为典型的气液固三相过程,通常采用的反应器为高压加氢釜。虽然加氢过程为快反应,但是加氢釜中由于气液固接触面积不足,存在较大的气液固传质阻力,导致加氢釜中完成加氢反应通常需要6~12 h,因此,工业生产中的加氢釜的体积通常比较大(1000~5000 L),反应时釜内滞存的大量高压氢气具有很大的安全隐患^[6]。同时,由于加氢釜是间歇操作,需要频繁置换气体,装卸催化剂等操作,人力需求多,并且当装卸钯碳或者雷尼镍等易燃性催化剂时,很容易引起安全事故^[7]。因此,发展安全高效的加氢技术是目前行业的迫切需求。

微反应连续流技术用于非均相催化加氢过程近几年得到了越来越多人的关注^[8-9]。微反应连续加氢过程可以提供更大的气液固相界面接触面积,极大强化气液固传质过程,提高催化剂的利用率,显著缩短加氢反应时间,减小反应器体积^[10-11]。通过催化剂固载或者在线过滤系统,可以避免催化剂的分离过程,提高操作安全性与简便性。微反应器内的液体流动是典型的平推流,可以减少甚至避免过度加氢等副产物的产生,提高反应的选择性^[12]。

本文阐述了近年来微反应连续加氢技术在有机合成领域内的发展,介绍了常用的反应器类型与催化剂的种类以及连续流技术在催化加氢反应中的实际应用。

1 连续流加氢反应器

在连续加氢过程中,通常通过将固体催化剂固定在反应器内部,使气液混合物连续地通过该反应器,与催化剂充分接触,从而实现优异的反应速率与高效的催化剂回收。按催化剂固定形式的不同,

可以分为填充式微反应器^[13]与壁载式微反应器^[14]。除此之外,通过将催化剂粉末悬浮在加氢底物中形成液体浆料,液体浆料同氢气混合通过微反应器的方式实现加氢过程的浆料式微反应器^[15]也是常用的连续流反应器。

1.1 填充式微反应器

填充式微反应器(又称微填充床反应器)[图1(a)]通过将颗粒催化剂以填充的形式固定在反应器内部的方式来实现非均相催化加氢反应。该反应器入口端通常安装或连接有气液混合装置,通过泵送气液混物流过固定催化剂的方式来实现气液固三相的有效接触,可以显著地强化传质过程,从而有效提高非均相反应的反应速率^[16]。该方法是目前文献报道中采用最多的技术路线^[17-19],具有催化剂易于更换和固定,操作简单高效等优点,同时也存在着多相流行为复杂、压降大和放大困难等问题。为了更精确地控制温度,以及确保装置可以在高压下运行,通常选择不锈钢作为该反应器的材质^[20]。

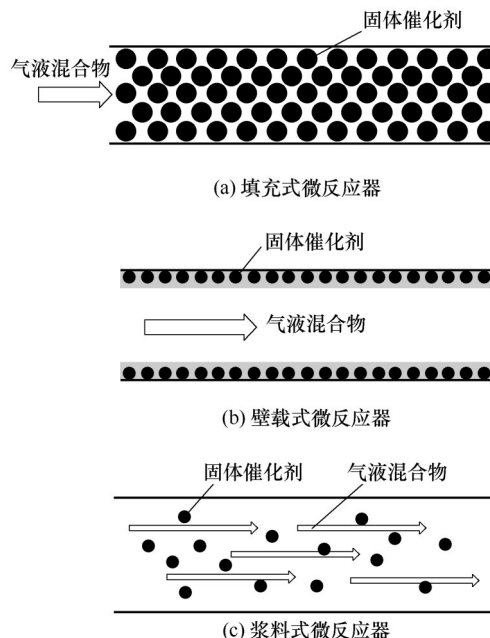


图1 三种典型连续流加氢反应器的示意图

Fig.1 Three typical flow reactors for continuous hydrogenation

1.2 壁载式微反应器

壁载式微反应器[图1(b)]将催化剂通过壁载的形式固定在反应器的内壁,气液混物流过反应器内部,与催化剂接触发生加氢反应。该方法具有流动简单、压降小和易于放大等优点,但也存在着单位体积催化剂浓度低、催化剂失活后难以更换等问

题。文献[14,21-23]报道通过将金属催化剂粉末以壁载的形式负载在玻璃板上得到加氢反应器,实现了强化气液固三相传质的效果,在2 min停留时间与室温反应条件下,利用Pd催化剂实现了碳碳双键与碳碳三键的高效选择加氢,收率高达97%^[22]。然而该装置具有金属催化剂易流失的缺点,将催化剂壁载在气相色谱的毛细管内可以有效地改善这一情况,并且通过增加反应器单元——毛细管柱的数量,可以实现有效的生产放大^[24-25]。澳洲CSIRO的研究者们^[26-27]利用金属3D打印构建复杂静态混合器,通过在静态混合器表面负载贵金属催化剂,可以有效提高反应器内单位体积催化剂浓度,提高加氢效果。

1.3 浆料式微反应器

浆料式微反应器[图1(c)]通过将固体催化剂粉末悬浮在液相中并与氢气混合,共同通入常规的微反应器中来实现非均相催化加氢反应。该方法具有催化效率高、压降低等优点,但如何保证催化剂均匀分散并保证催化剂的高效性及稳定性,同时实现催化剂的连续分离和分散是该路线的难点。Buisson等^[15]利用浆料式微反应器强化了传质与传热效果,在1 min停留时间、更低的催化剂负载量的实验条件下,实现了与釜式反应器中相同的加氢选择性,140℃时,转化率达到了98.9%。

2 常用的固体加氢催化剂

许多金属元素及其氧化物被证实具有一定的加氢活性,如Fe、Co、Ni、Cu、Zn以及贵金属元素Pd、Pt、Ru、Rh等^[20]。在实际应用中,通常将加氢催化剂负载在具有一定机械强度与化学稳定性的载体上进行使用。常用的负载型催化剂的制备方法有浸渍法^[28-30],溶胶凝胶法^[31-33],沉积-沉淀法^[34-36]与离子交换法^[37-39]等。

在加氢领域中,Pd/C催化剂具有高比表面积,强吸氢能力的优势,因此被普遍应用^[40]。Yang等^[41]利用Pd/C催化剂进行了木质素中醚键的氢解,并且与Pt/C、Ru/C催化剂相比较,显示了Pd/C优秀的氢化活性。然而Pd/C催化剂极易自燃,具有一定的安全隐患。Byun等^[42]通过沉积-沉淀法制得Pd/Al₂O₃催化剂进行了马来酸的氢化,结果表明该催化剂加氢活性较高,且能避免催化剂易自燃的危险。Ma等^[43]制备了二氧化硅/壳聚糖负载Pd的核壳结构催

化剂,具有高的比表面积、优秀的热稳定性与化学稳定性以及一定的机械强度,实现了环己烯高效加氢。此外,雷尼镍也是常用的加氢催化剂之一^[44-45],具有较高的活性,但是易自燃,需要在氮气气氛下进行保存。

3 连续流反应器中的催化加氢反应

3.1 碳碳双键与三键氢化

3.1.1 烯烃加氢 烯烃类物质的加氢是一种容易进行但具有重要意义的反应类型,高效与高选择性的进行烯烃的催化加氢具有巨大的价值。已经有大量文献阐述了利用连续流反应器来探索烯烃加氢反应。由于环己烯本身结构较为简单,常被选择为该类型加氢反应的底物。Bakker等^[25]利用壁载毛细管反应器克服了三相传质阻力后,采用Pd/Al₂O₃作为催化剂,实现了较高反应速率的环己烯加氢反应,停留时间(*t*)只需要12 s,收率达到99%[图2(a)]。Linares等^[46]在连续流反应器中采用Pd/TiO₂催化剂催化加氢环己烯,观察到了相似的结果,单位活性位在单位时间内转化的反应物的量(TOF)为1131 h⁻¹[图2(b)]。Hitzler等^[47]探索了连续流反应器在加氢选择性上的优势,他们利用装填微米级尺寸(300~800 μm)的5.7%(质量) Pd/氨基聚硅氧烷催化剂颗粒(Pd/Deloxan)的微填充床反应器进行了异佛尔酮的选择性加氢实验,(反应流程如图3所示),在合适的反应条件下,实现了产物3,3,5-三甲基环己酮约90%的较高选择性[图2(c)]。

3.1.2 炔烃加氢 烯烃类物质是生物学上的重要

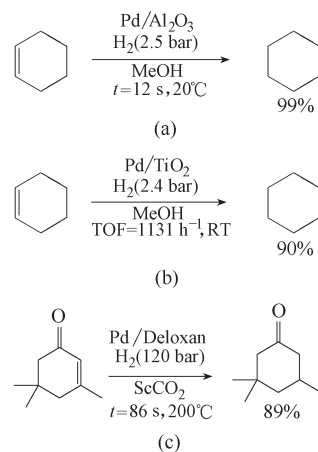
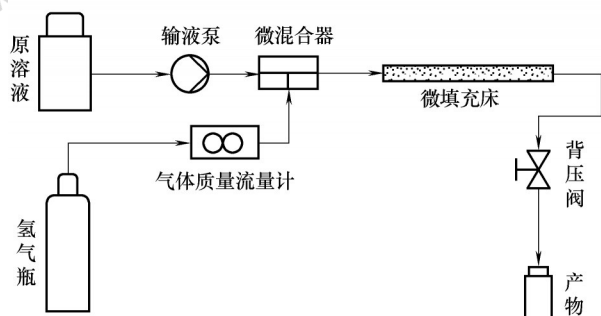
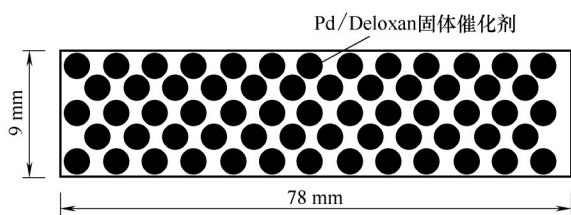


图2 碳碳双键的连续加氢

Fig.2 Continuous hydrogenation of carbon-carbon double bonds(1 bar=0.1 MPa)



(a) 异佛尔酮的选择性加氢



(b) 填充床反应器结构

图 3 微填充床反应器中的加氢流程

Fig.3 Hydrogenation in micro-packed bed reactor

结构,常被用于药物与香料等物质中。由炔烃类物质部分加氢的方式是制备烯烃类物质的常用方法,然而如何有效地按需合成顺反结构的烯烃是需要考虑的问题之一。通过研究炔烃的催化加氢过程,可以直观地发现连续流反应器对于碳碳三键加氢反应具有增强反应速率与提高加氢选择性的优势。Zhou 等^[48]通过沉积-沉淀法制得了 Pd/TiO₂ 催化剂,并将其填充在连续流反应器中进行丙炔的非均相加氢,实验结果表明,在连续流反应器中,低的氢气/丙炔比与高温条件有利于丙炔的顺式加成与部分还原[图 4(a)]。Rehm 等^[49]通过具有高气液接触面积的降膜反应器(壁载型反应器)实现了 2-丁炔-1,4-二醇的选择性氢化得到反式 2-丁烯-1,4-二醇,丁炔二醇转化率高达 96% 与产物选择性达到 98%,表现出了远优于间歇式反应器的性能[图 4(b)]。Moreno-Marrodan 等^[50]在微填充床反应器中进行了多种含可还原基团结构的炔烃类物质的选择性加氢实验,结果表明连续加氢技术可以通过及时在催化剂活性位点上移除目标产物的方式来避免过度加氢。与通过减弱催化剂活性来抑制过度加氢的间歇式反应器相比,连续加氢技术更适用于炔烃类物质的按需加氢。

3.2 羰基加氢

3.2.1 醛类物质氢化 利用醛类化合物的还原来

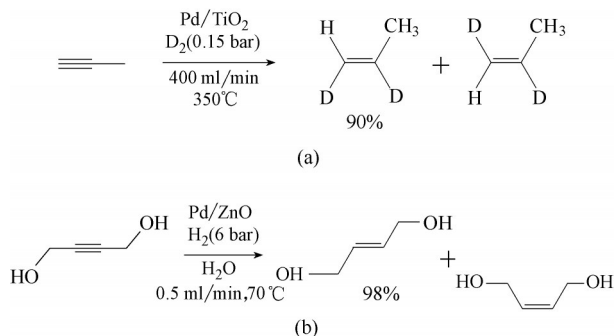


图 4 碳碳叁键的连续加氢

Fig.4 Continuous hydrogenation of carbon-carbon triple bonds

得到目标醇一直是化学化工中常用的方法之一,如何在其他还原性基团,特别是酮基存在的前提下,对醛基进行选择性地还原是化学工作者们时常遇到的问题。Osako 等^[51]开发了一个连续加氢系统,将制备的负载在两亲性树脂上的 Pt 催化剂(ARP-Pt)填充在微填充床反应器中,实现了停留时间 22 s 内多种含酮基的醛类化合物的高选择性加氢[图 5(a), (b)]。Bai 等^[52]研究了肉桂醛的选择性催化加氢,开发了一个壁载有 190 mg 12%(质量) Pt/SiO₂ 催化剂涂层的连续流反应器,可以有效防止氢化肉桂醛与氢化肉桂醇的产生,从而定向得到所需的肉桂醇(反应流程如图 6 所示),在 98.8% 的高转化率的同时,选择性高达 90%[图 5(c)]。与间歇式反应器相比较,在相同温度压力以及催化剂用量情况下长周期(110 h)地工作时,利用该壁载型反应器得到的肉桂醇产量约是间歇式反应器内产量的 7.5 倍,体现了连

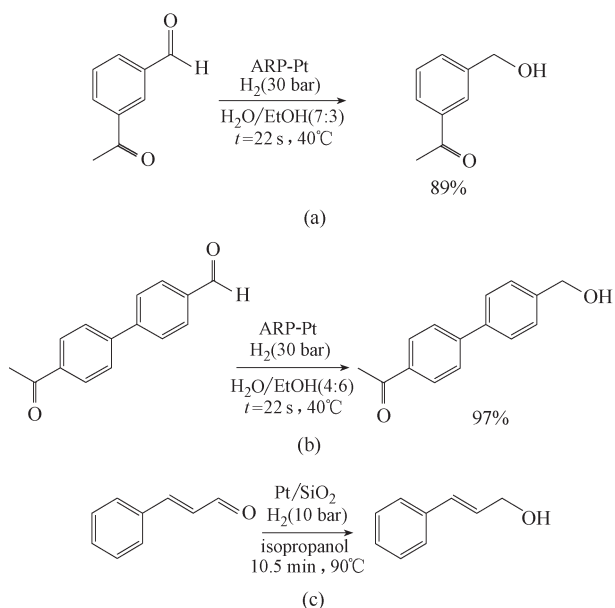


图 5 醛类物质的连续加氢

Fig.5 Continuous hydrogenation of aldehydes

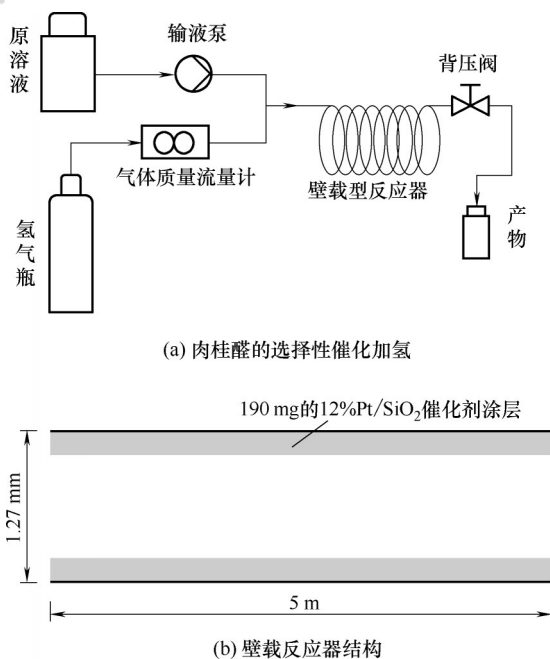


图6 催化剂涂层管式反应器中的加氢流程

Fig.6 Hydrogenation in catalyst-coated tube reactor

续流反应器应用于醛类物质选择性加氢的巨大优势。

3.2.2 酮类物质氢化 直接还原酮类物质来得到目标醇也是常用的具有原子经济性的绿色方法之一,譬如苯乙酮还原得到 α -苯乙醇常用于镇痛与消炎药物的制备^[53]。Molinari等^[54]开发了一个将Pd负载在FAU分子筛上的连续流膜反应器,实现了苯乙酮的高效非均相还原,得到了70%的收率,远高于在间歇式反应器内的35%收率[图7(a)]。受阻胺光稳定剂是橡胶,塑料工业中一种重要的化合物,其中间体四甲基哌啶醇可以由三丙酮胺直接加氢还原得到。与常用的釜式反应器相比较,Fan等^[20,55]利用一种可以高效还原三丙酮胺的Cu-Cr/Al₂O₃微填充床反应器,实现了四甲基哌啶醇的快速制备,得到了90%的高收率[图7(b)]。

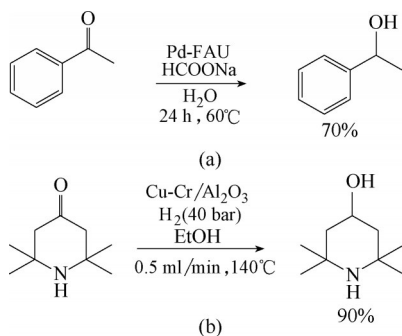


图7 酮类物质的连续加氢

Fig.7 Continuous hydrogenation of ketones

3.3 亚胺和腈基氢化

3.3.1 亚胺氢化 还原胺化反应是常用的合成医药中间体的方法之一,在羰基与胺类物质反应生成亚胺后,需要用还原剂对亚胺中间体进行氢化。在亚胺的还原制得仲胺的过程中,通常会产生被过度还原而得到的伯胺,芳基亚胺的过度还原甚至会产生不必要的脱苄基(Bn)反应。为了有效地防止过度加氢,Saaby等^[56]在商业化的实验室H-Cube反应器中进行了多种亚胺(含氰基等其他官能团)还原制备仲胺的实验探索,使用10%Pd/C催化剂,室温,2 MPa反应条件的情况下,均得到了较高的仲胺收率[图8(a),(b)]。Clark等^[13]利用微填充床反应器,使用Pd/CaCO₃催化剂催化还原药物中间体-舍曲林亚胺以制备盐酸舍曲林,实现了99%转化率与97%以上的顺式产物化学选择性,与间歇式反应器相比较,能有效地避免副反应的产生[图8(c)]。

3.3.2 腈基氢化 在有机化学合成中,利用腈基类物质的充分还原是得到伯胺,尤其是二胺类物质的常用办法^[57]。在腈基还原的过程中,存在着反应中间体通过缩合反应引入仲胺与叔胺杂质的情况,如何高选择性地实现腈基的还原,是需要被考虑的问题之一^[58]。Saito等^[59]开发了一个装填聚硅烷/SiO₂负载钨催化剂的微填充床反应器,实现了芳香腈,脂肪腈与苄基氰化物类物质的选择性高效还原,得到了目标伯胺,收率均在90%以上,有效防止了仲胺与叔胺的形成[图9(a)]。Labesa等^[60]利用Ru催化剂在连续流反应器中也观察到了相似的结果,多种腈基类物质还原后,均得到了高产量的伯胺[图9(b)]。

3.4 硝基加氢

在药物,除草剂以及塑料工业中,功能化的苯胺类物质是一类重要的中间体^[61],通常可以由硝基化合物直接加氢制得。然而在其他还原性官能团存在的情况下,如何快速,高选择性地还原硝基具有重要的研究意义与实际价值。已经有大量的工作证实,连续流加氢装置对于硝基的快速氢化具有明显的优势。Baumann等^[62]利用H-Cube反应器在常压下利用雷尼镍催化剂实现了含多种N-Bn结构的硝基吡咯烷的加氢,选择性均在90%以上[图10(a)]。Howard等^[63]成功利用Pd/C催化剂实现了通过硝基的连续加氢来获得抗肿瘤药物的前体药物,选择性达到81%[图10(b)]。此外,Jones^[64]等在H-Cube反应器中也实现了硝基类物质的2 min停留时

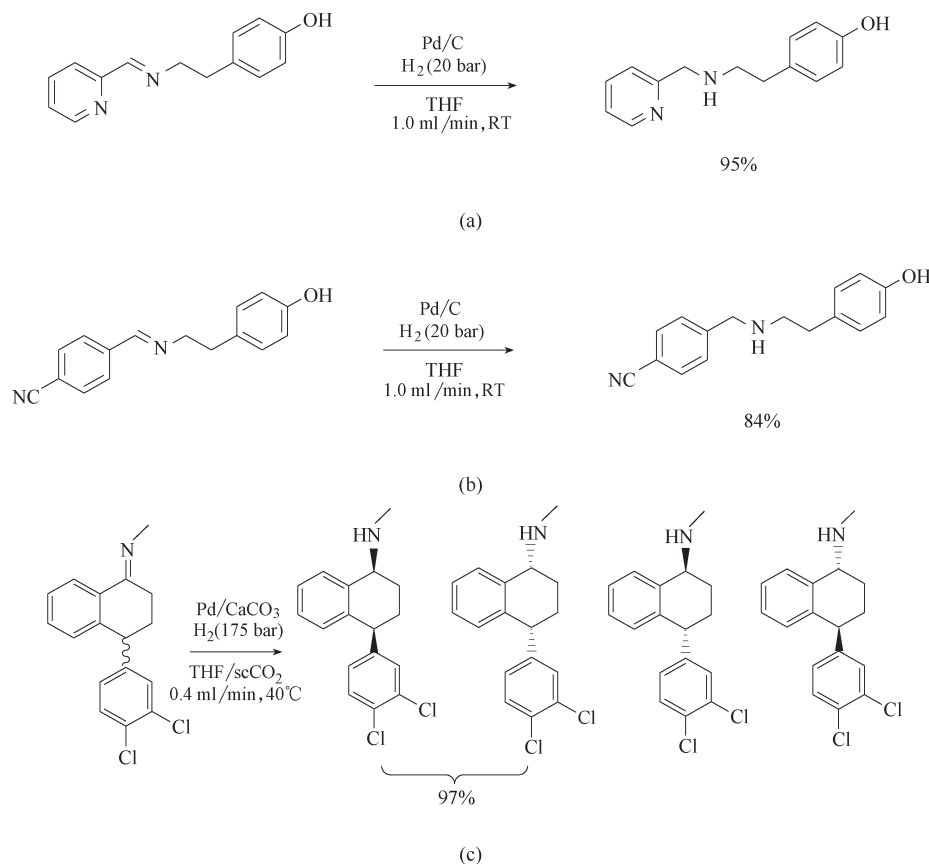


图8 亚胺类物质的连续加氢

Fig.8 Continuous hydrogenation of imines

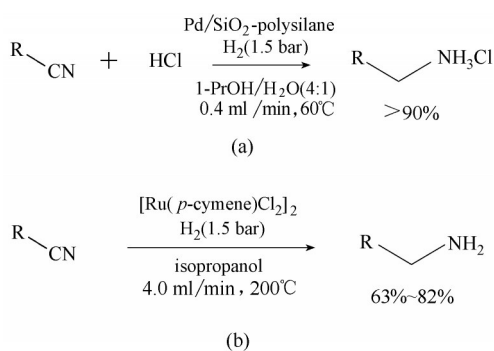


图9 腈类物质的连续加氢

Fig.9 Continuous hydrogenation of nitriles

间内的快速氢化,结果都证实了H-Cube反应器在硝基加氢过程中的具有强化反应速率的巨大优势[图10(c)]。

3.5 脱保护反应

3.5.1 脱苄基反应 苄基类保护基团在有机合成反应中,常被合成为苄醚、苄醇、苄胺与苄酯类物质^[65]用以保护羟基、氨基等一些较为活泼的基团。据估计,超过1000种药物合成过程中需进行脱苄基反应^[40]。Desai等^[66]在H-Cube反应器中,利用Pd/C催化剂实现了存在酰胺键与碳碳双键等干扰基团

的情况下连续脱Bn,选择性高达95%[图11(a)]。Matos等^[67]也在填充床反应器中实现了大环内脂结构物质的多个苄基的脱除,选择性达到了89%(图11(b))。Akiem团队^[68]利用连续流反应器实现了在二氧化碳气体促进下,利用Pd/C、Pd/CaCO₃以及Pd/Deloxan多种催化剂实现了连续流反应器中1,4-二苄氧基苯的高效定向脱苄,原料的转化率与产物的选择性均达到86%以上[图10(c)]。这些结果均显示了连续加氢装置在脱苄基反应上的巨大优势。

3.5.2 脱苄氧基羰基(Cbz)反应 与Bn类似,Cbz也是一类常用于保护醇,硫醇,胺和羧酸物质的保护基团,可以直接利用H₂进行脱除^[69]。Franckevičius等^[70]在H-Cube反应器中,利用10%的Pd/C催化剂,实现了常压下(S)-2-(1H-四唑-5-基)吡咯烷-1-羧酸苄酯的快速脱Cbz反应,在底物中存在叠氮与亚胺结构的情况下,脱Cbz的选择性达到了98%[图12(a)]。Duthion等^[71]在β肾上腺素能受体阻滞剂制备的过程中,成功利用连续流反应器进行了中间产物的脱Cbz反应[图12(b)],得到了较好的收率。这些结果均显示出了连续加氢在脱Cbz反

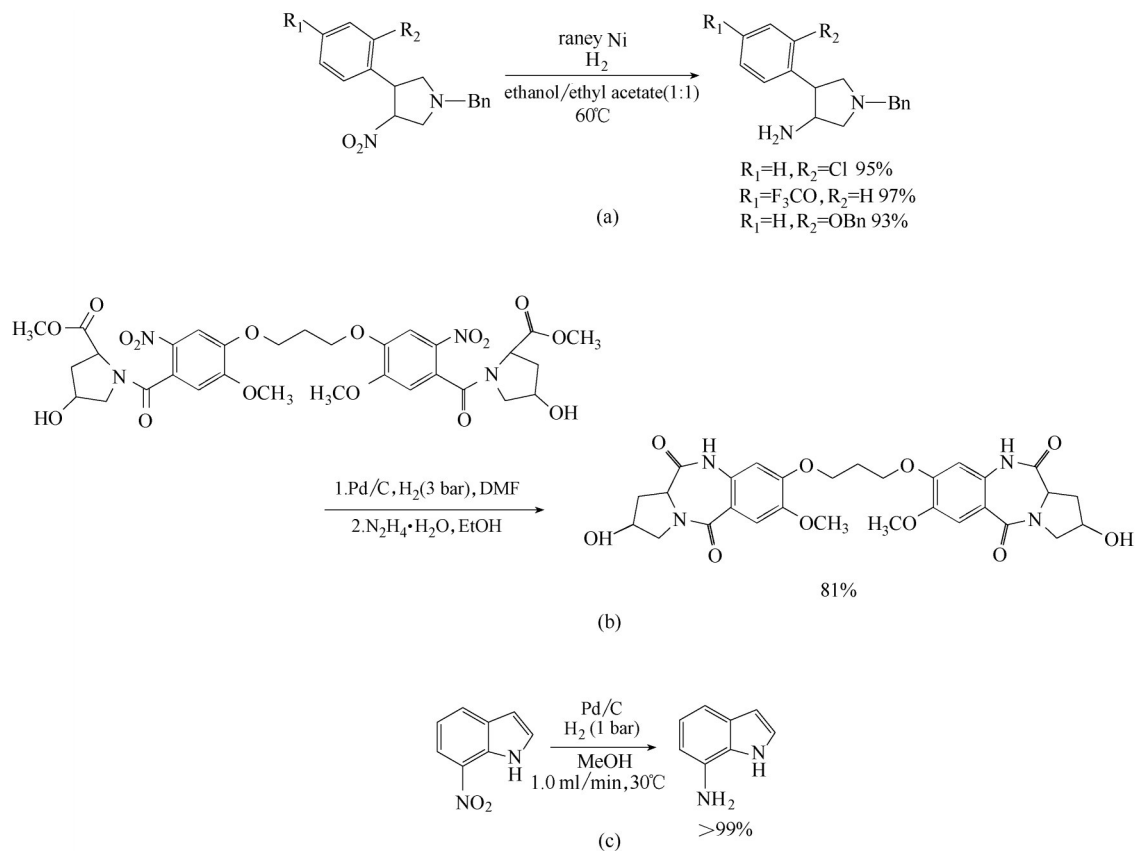


图10 硝基的连续加氢

Fig.10 Continuous hydrogenation of nitro

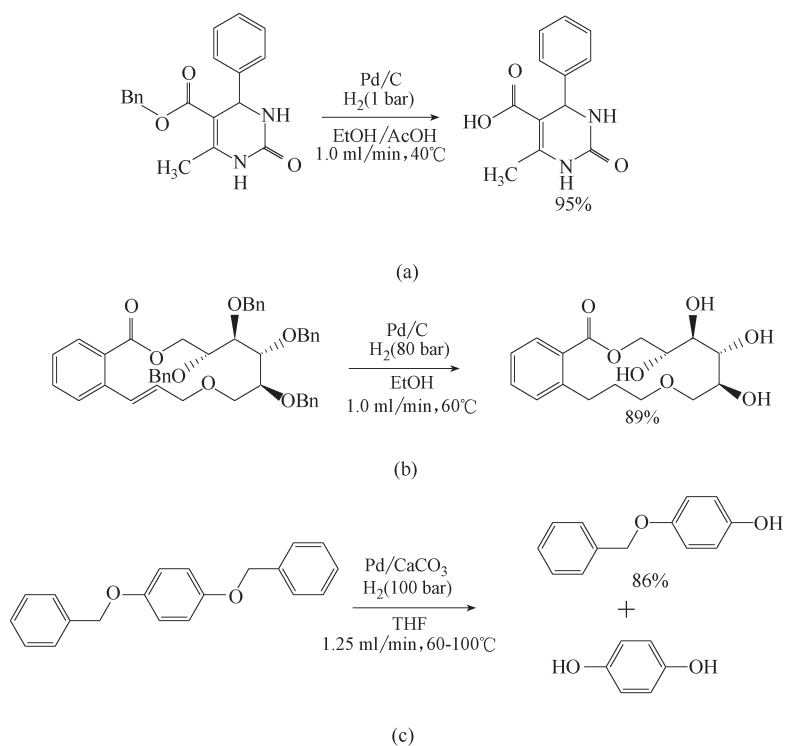


图11 连续加氢脱苄基反应

Fig.11 Continuous hydrodebenzylation reaction

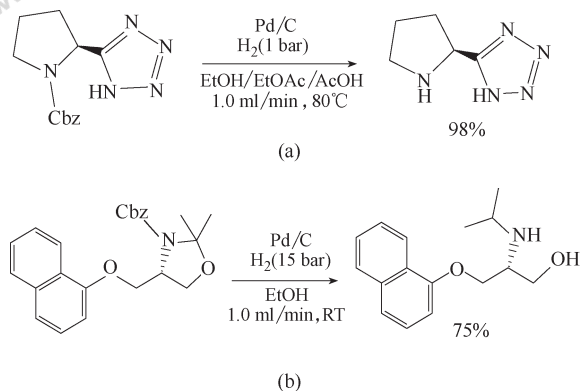


图 12 连续流动下脱 Cbz 保护基反应

Fig.12 Protecting group removal under continuous flow conditions

上的优势。

4 结论与展望

连续加氢反应器由于能提供更大的气液固三相接触面积,更短的传质距离,以及及时从系统中移除产物以避免过度加氢产生不必要的副产物,因此表现出了比间歇式反应器更加优秀的加氢性能。此外连续加氢技术采用固体催化剂与 H_2 为氢供体而不是均相催化的方式,可以简便有效地进行催化剂的回收利用以及产物的提纯分离,更加符合绿色化学的原则。该技术的发展,能满足精细化工对于产品工艺的选择性与生产效率的更高需求。但是目前该技术还面临着微尺度下多相流认识不清,反应器放大困难以及跟微反应器匹配的催化剂制备困难和商业化选择较少等困难。因此,目前该技术更多应用于实验室规模的科学研究,在较大规模上的工业应用报道仍然较少。作者所在的研究团队在多年研究的基础上,在2018年成功实现了脱苄基、硝基加氢等多个反应类型的吨级和百吨级产品的生产,相对于传统釜式加氢在安全、效率和成本上具有明显的优势。因此,我们相信随着该技术的进步,未来连续微反应加氢技术在精细化工领域的应用也必将更为广泛。

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