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镍催化惰性碳氢键活化研究进展

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摘要 相较于传统的偶联反应，碳氢键活化由于无需预官能团化，而具有相对更高的原子经济性和环境友好性，近年来广受关注，并取得迅猛发展．钯、铑、钌和铱等贵金属催化的碳氢键活化近年来已经取得了令人瞩目的发展，但较高的催化剂成本以及有毒有害的重金属残留在一定程度上也限制了其应用．因此，以储量丰富并且价格相对低廉的铁、钴、镍和铜等廉价金属为催化剂，实现惰性碳氢键活化具有重要的科学价值和经济意义．由于镍催化剂价格相对低廉并且具有良好的催化活性，近年来，镍催化的惰性碳氢键活化受到广泛关注．本文综述了镍催化的惰性碳氢键活化的最新研究进展，并对催化体系、成键类型和反应机理进行了初步探讨．

关键词
碳氢键活化
镍
官能团化
惰性

近年来，过渡金属催化的碳氢键活化广受关注，并取得迅猛发展[1~4]．相对于传统的偶联反应，碳氢键活化由于无需预官能团化，而具有相对更高的原子经济性和环境友好性[5]，目前已逐渐被应用到药物分子、天然产物以及功能材料的合成上，提高了合成效率并降低了成本．

钯、铑、钌和铱等贵金属催化的碳氢键活化近年来已经取得了令人瞩目的发展，但较高的催化剂成本以及有毒有害的重金属残留在一定程度上也限制了其应用．因此，以储量丰富并且价格相对低廉的铁、钴、镍和铜等廉价金属为催化剂，实现惰性碳氢键活化具有重要的科学价值和经济意义．廉价过渡金属镍虽然在传统偶联反应和催化烯烃或者炔烃的聚合反应中已经取得了飞速发展，并体现出独特的催化活性，但是相对于贵金属催化的碳氢键活化，其研究仍然处在起步阶段[6,7]．因此，发展镍催化的惰性碳氢键活化方法，无论在有机化学理论的发展还是在化学工业的应用上都将具有重要的意义．本文将系统介绍近年来镍催化的惰性碳氢键活化研究进展，并按照被活化的碳氢键杂化类型和成键类型进行分类．对于镍催化的活泼碳氢键活化，已有综述进行了介绍，这里不再赘述[8,9]．

1 镍催化的C(sp^2)–H键活化

1.1 碳碳键的形成

2011年，Chatani课题组[10]报道了零价镍催化的苯甲酰胺与炔烃的氧化环加成反应，该反应具有良好的底物普适性和区域选择性(图1)．当使用不对称的炔烃时，反应也具有很高的选择性，如果使用苯基和烷基取代的炔烃，在产物中苯基所连的碳原子更靠近氮原子；此外，芳环上取代基的电子效应也对选择性有一定的影响，供电基团的选择性较吸电基团高．

2013年，Chatani课题组[11]报道了镍催化8-氨基喹啉[12~16]导向的苯甲酰胺和烷基卤化物的烷基化反应(图2(a))．该反应对许多官能团都有很好的容忍性，碘代烷烃和溴代烷烃都能以良好的产率得到烷基化产物(**6aa**，**6ab**)．然而当以氯代烷烃进行烷基化反应

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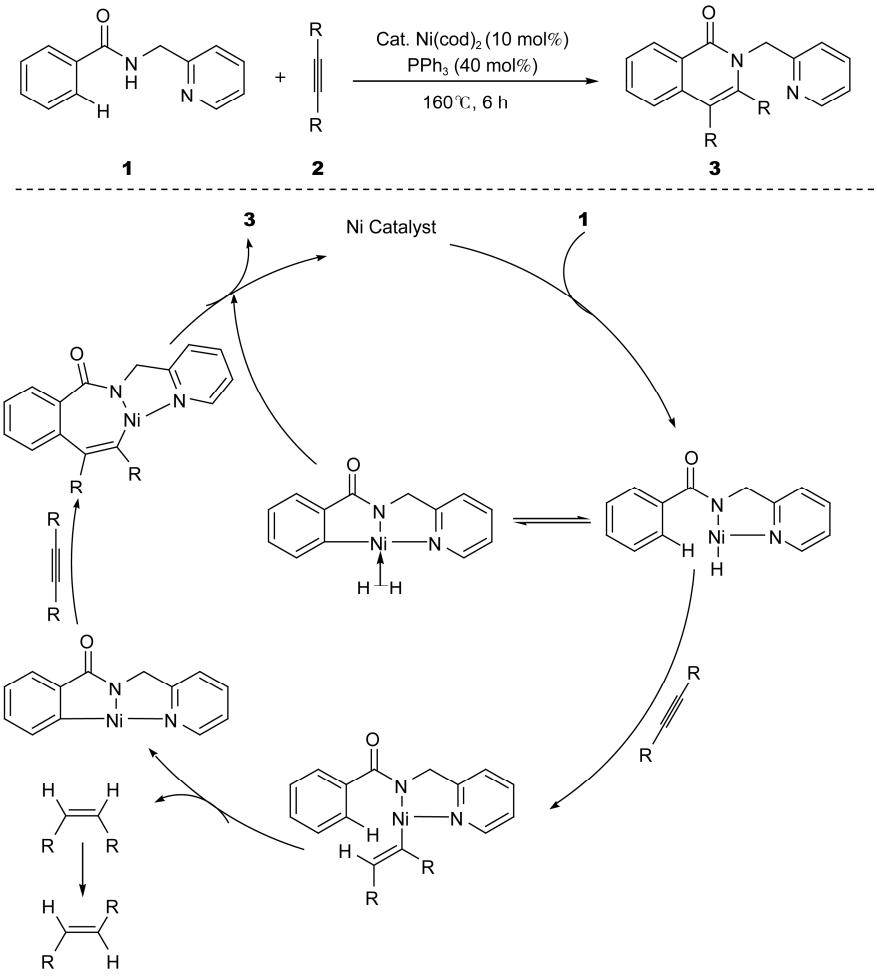

图 1 零价镍催化的苯甲酰胺与炔烃的氧化环加成

Figure 1 Ni(0)-catalyzed oxidative annulation of benzamides with alkynes

时，没有得到产物，加入碘盐后产物产率提高至88%(**6ac**). 不考虑取代基的电子性质，反应的区域选择性是由取代基的位阻效应所控制的(**6b~6d**)，吸电子基取代的苯甲酰胺的烷基化产物产率较高. 此外，β-烯基碳氢键也能够活化，从而也适用于α,β-不饱和酰胺类底物. 2014年，Chatani课题组[17]也报道了镍催化8-氨基喹啉导向的芳酰胺碳氢键的芳基化反应.

2014年，Ackermann课题组[18]报道了8-氨基喹啉导向的镍催化苯甲酰胺与二级卤代烷烃的烷基化和三氟乙基化反应(图2(b)). 该烷基化反应对各种官能团具有很好的容忍性，并且产物能够获得令人满意的收率(**9a~9d**). 当以三氟碘乙烷为烷基化试剂时，可以得到中等到良好产率的三氟乙基化产物(**12a~12c**).

2014年，同样以8-氨基喹啉为导向基，Zeng课题组[19]报道了镍催化的芳基碳氢键与烯丙基磷酸酯的偶联反应(图3(a))，该镍催化剂高效地催化碳氢键的烯丙基化反应，并且反应主要由位阻效应控制. 该反应提供了一种由易获得的苯甲酰胺和芳基磷酸酯选择性地高效制备直链烯丙基芳烃的方法，产率最高可达98%.

2014年，Chatani课题组[20]报道了Ni(II)催化5-氯-8-氨基喹啉导向的芳环C(sp^2)–H键与苄位C(sp^3)–H键的氧化偶联反应(图3(b)). 在该反应中，惰性的叔丁基苯作为溶剂，甲苯及其衍生物作为偶联试剂与苯甲酰胺反应，而且七氟异丙碘对于反应是必不可少的. 该方法具有很广的适用性，并且对很多官能团(如甲基、甲氧基、卤素和三氟甲基等)均有很好的容忍性，反应产物产率最高达91%.

本课题组[21]最近发展了一类具有偕二甲基效应

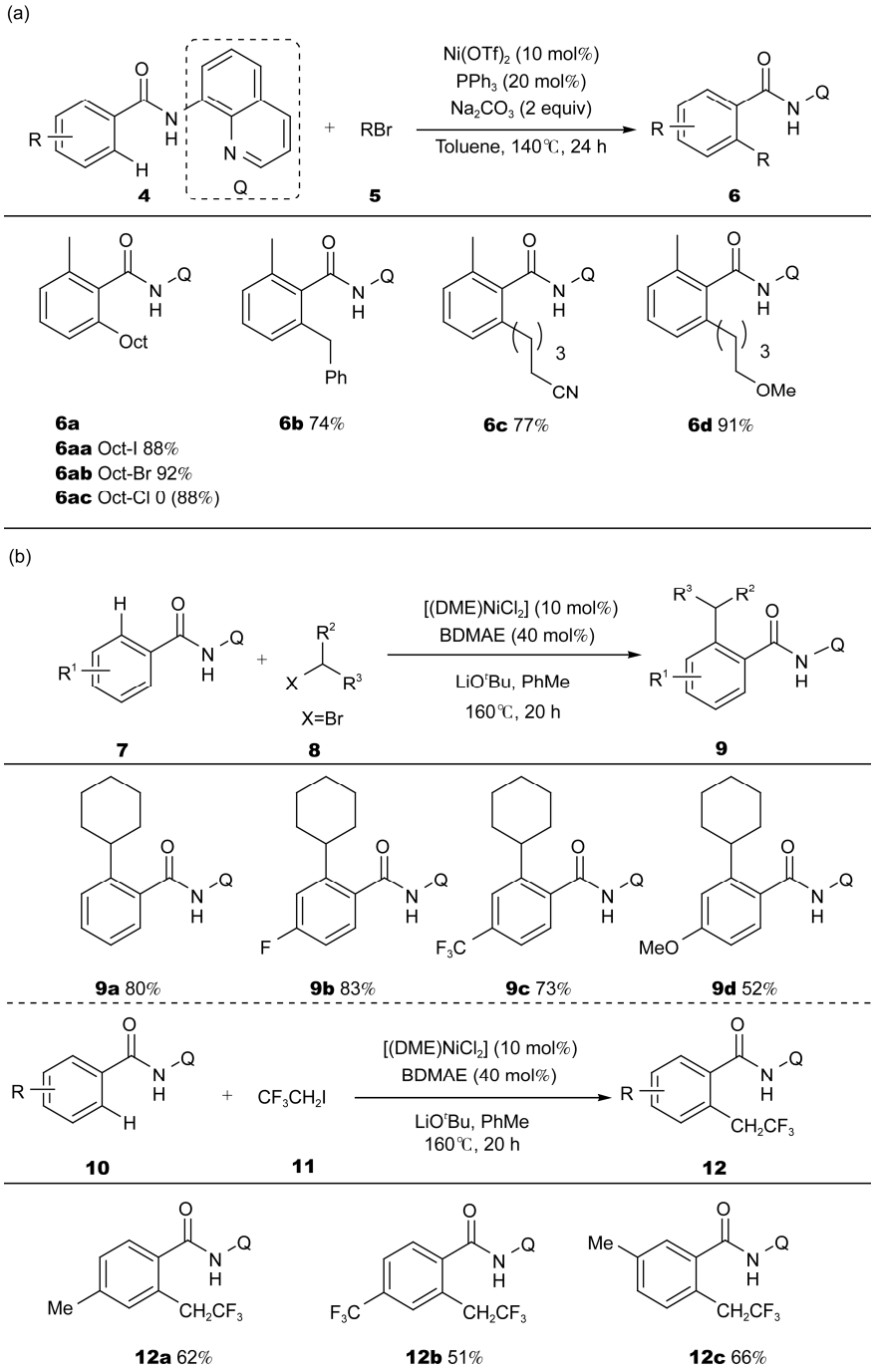

图 2 Chatani 课题组(a)和 Ackermann 课题组(b)报道的镍催化 C(sp^2)–H 键的烷基化反应

Figure 2 Ni-catalyzed alkylation of C(sp^2)–H bonds by Chatani group (a) and Ackermann group (b)

的新型双齿导向基2-吡啶基异丙胺(PIP)，利用该导向基团，我们成功地实现了钯催化的亚甲基sp^3碳氢键活化[21~23]，进一步的研究表明，PIP导向基团也能促进廉价金属铜催化的惰性碳氢键活化[24~29]. 基于以上研究结果，本课题组[30]最近实现了以PIP为双齿导向基团镍催化芳环C(sp^2)–H键的炔基化反应(图3(c)). 该反应具有以下显著的特点：(1) 催化体系简单，无需任何配体和氧化剂；(2) 较低的催化剂用量(0.5%摩尔当量镍催化剂)和高转化数(TON最高196)；(3) 高底物的适用性和官能团容忍性，各种取代的芳

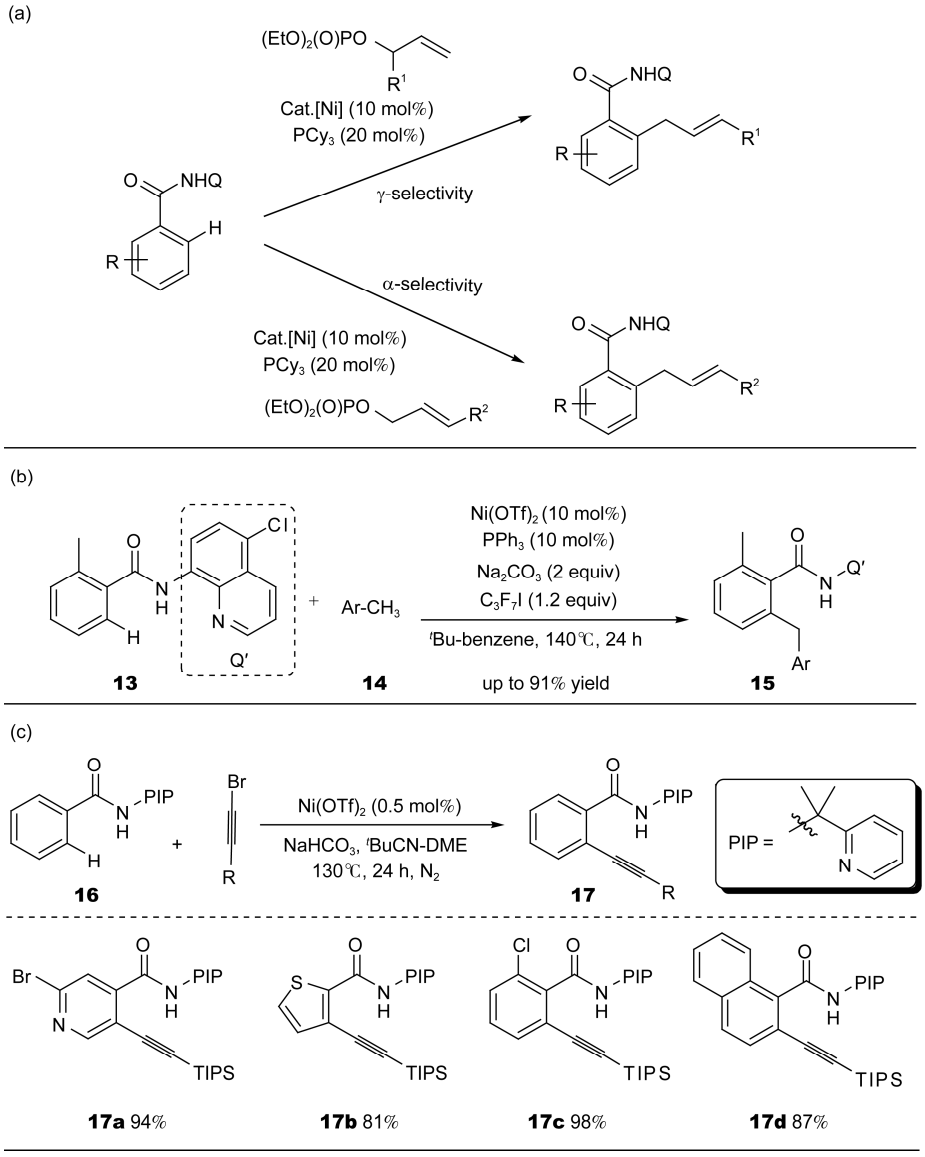

图 3 (a) Zeng 课题组报道的镍催化 C(sp^2)–H 键的烯丙基化反应; (b) Chatani 课题组报道的镍催化芳环 C(sp^2)–H 与苄位 C(sp^3)–H 的氧化偶联反应; (c) 本课题组报道的镍催化 C(sp^2)–H 键的炔基化反应

Figure 3 (a) Ni-catalyzed allylation of C(sp^2)–H bonds by Zeng group; (b) Ni-catalyzed dehydragenative coupling of aromatic C(sp^2)–H with benzylic C(sp^3)–H by Chatani group; (c) Ni-catalyzed alkynylation of C(sp^2)–H bonds by our group

(杂)环都能够进行反应并且得到较高的产率.

2013年, Ackermann课题组[31]报道了镍催化的苯胺类化合物与炔烃的环化反应(图4). 利用该反应通过碳氢键/氮氢键的官能团化能够合成吲哚类化合物. 他们发现无论是带有供电基团还是吸电基团的二苯乙炔衍生物都能与苯胺类化合物高效地进行反应, 产物的产率中等(**20a~20e**), 该催化体系不仅仅只适用于二苯乙炔衍生物, 取代的烷基炔烃也能够很好地进行反应(**20f**, **20g**). 与传统的使用贵金属铑、钯和钌催化剂催化合成吲哚类化合物相比, 该反应具有以下3个优点: (1) 该反应利用的是易除去的单齿导向基; (2) 对于富电子的苯胺类化合物依然具有很高的催化效率; (3) 氧化炔烃环化反应不需要外加铜盐或者银盐作为氧化剂.

2015年, Ge课题组[32]报道了镍和铜协同催化的C(sp^2)–H键的羰基化反应(图5), 该反应使用*N*,*N*-二甲基甲酰胺(DMF)作为羰基的来源. C(sp^2)–H键的羰基化反应表现出了很好的区域选择性和官能团容忍

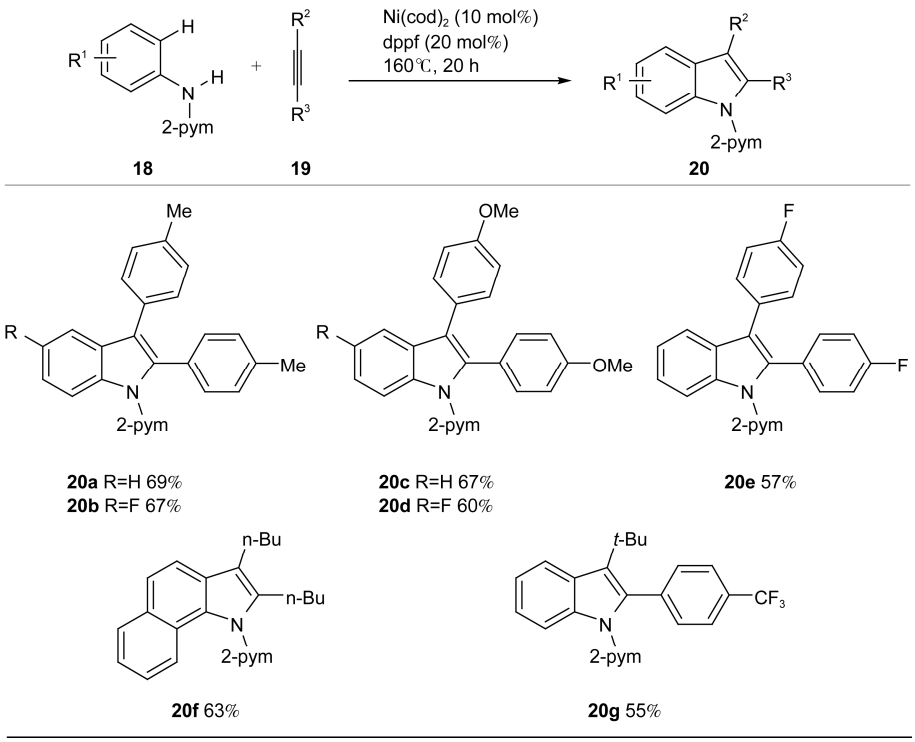

图 4 镍催化的苯胺类化合物与炔烃的环化反应

Figure 4 Ni-catalyzed cyclization of anilines with alkynes

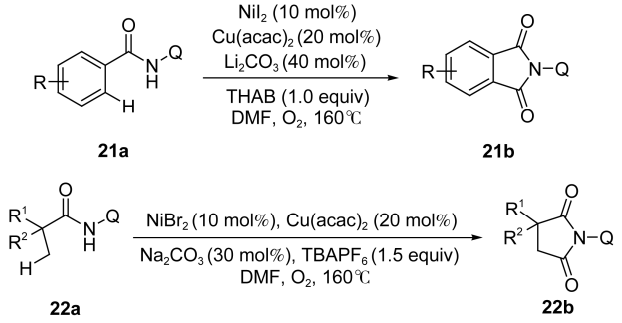

图 5 镍/铜协同催化的惰性 C–H 键活化/羰基化反应

Figure 5 Ni/Cu-cocatalyzed carbonylation of unactivated C–H bonds

性，供电子基取代的底物反应产物的产率较高.

1.2 碳硫键的形成

2015年，本课题组[33]报道了PIP导向镍催化惰性C(sp^2)–H键的硫醚化反应(图6(a)). 该反应对各种官能团具有很好的容忍性，并且对杂环底物同样适用. Lu课题组[34]也报道了类似的反应.

几乎与此同时，Zhang课题组[35]和Shi课题组[36]分别报道了镍催化的8-氨基喹啉导向的芳烃和烯烃的硫醚化反应(图6(b)和(c)). 无论是富电子还是缺电子基取代的底物都能很好地进行反应得到较高的产率，并且烯基碳氢键也能够顺利的进行反应.

2 镍催化的C(sp^3)–H键活化

2.1 碳碳键的形成

2014年，Ge课题组[37]报道了8-氨基喹啉导向的镍催化的惰性C(sp^3)–H键的烷基化反应，该反应的底物类型局限于α位为季碳的酰胺(图7(a)). 如果在反应体系中加入CsI，溴代或者是氯代烷烃可以代替碘代烷烃进行反应，该反应对各种官能团(烯基、酯基和三氟甲基等)都具有很好的容忍性. 同年，Chatani课题组[38,39]报道了镍催化的8-氨基喹啉导向的脂肪族酰胺C(sp^3)–H键的芳基化反应(图7(b)). You课题组[40]报道了8-氨基喹啉导向镍催化的惰性C(sp^3)–H键的芳基化反应(图7(c)).

最近，本课题组[41]报道了镍催化的惰性C(sp^3)–H键的烯基化反应(图8). 该反应使用廉价且在空气中非常稳定的乙酰丙酮镍作为催化剂，联萘酚为配体，能够高效地促进一系列脂肪族甲酰胺β甲基C(sp^3)–H键的烯基化反应，并且得到的产品还可以进行下一

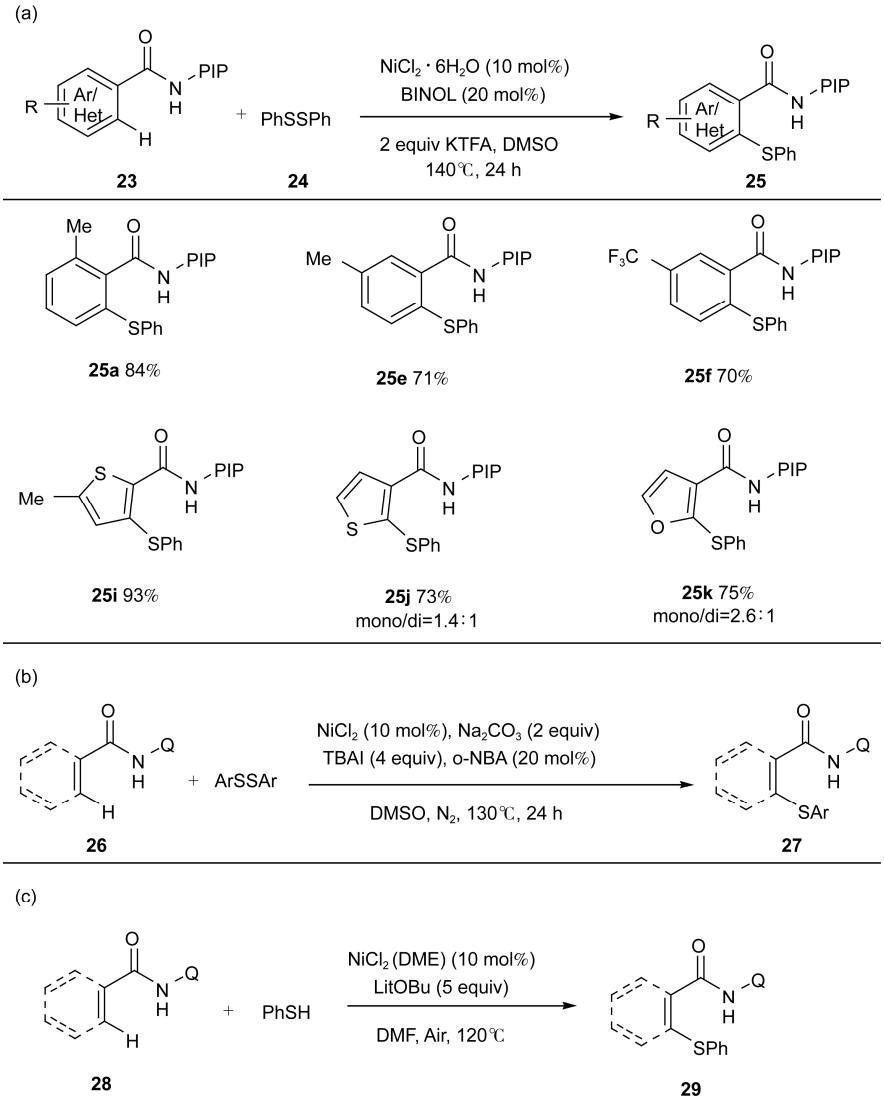

图 6 本课题组(a)、Zhang 课题组(b)和 Shi 课题组(c)报道的镍催化 C(sp^2)–H 活化/C–S 键形成反应

Figure 6 Ni-catalyzed thiolation of C(sp^2)–H bonds by Zhang group (a), Shi group (b) and our group (c)

步碳氢键的官能团化. 该反应产物收率中等, 反应发生在酰胺邻位甲基C(sp^3)–H键而非亚甲基或苄基的C(sp^3)–H键上(**40a**, **40b**, **40e**), 酰胺邻位碳原子取代基的位阻越大, 产物的收率越低.

2.2 碳氮键的形成

2014年, Ge课题组[42]报道了镍催化8-氨基喹啉导向的惰性C(sp^3)–H键分子内酰胺化反应(图9). 该反应对官能团具有很好的容忍性, 在双齿导向基与镍催化剂的作用下, 脂肪族酰胺β位惰性C(sp^3)–H键能够发生分子内脱氢环化反应.

Ge课题组[32]报道了镍和铜协同催化C(sp^3)–H键的羰基化反应(图5), 该反应使用DMF作为羰基的来源.

2.3 碳硫键的形成

最近, Zhang课题组[43]、Shi课题组[36]、Qiu课题组[44]和本课题组[45]几乎同时报道了镍催化的8-氨基喹啉导向的脂肪族酰胺C(sp^3)–H键的硫醚化反应(图10). 尽管反应条件迥异, 但是反应的底物类型都同样局限于反应α位为季碳的酰胺. 反应主要发生在甲基C(sp^3)–H键而非亚甲基的C(sp^3)–H键. 发现富电子取代的二硫化物得到的产品产率相对较高; 酰胺α位碳原子取代基的位阻越大, 产物的收率越低.

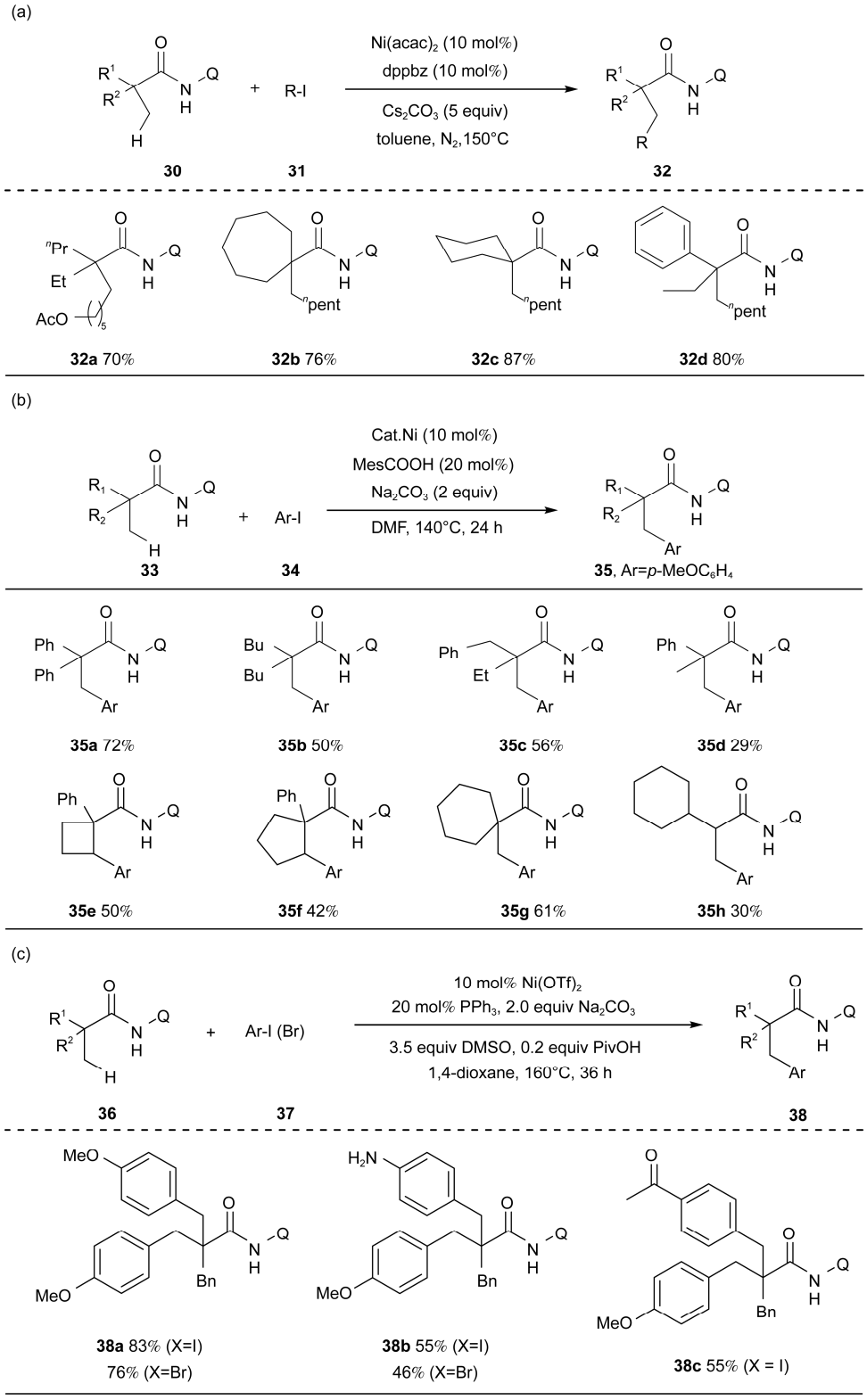

图 7 (a) Ge 课题组报道的镍催化 C(sp^3)–H 键的烷基化反应; (b) Chatani 课题组报道的镍催化 C(sp^3)–H 键的芳基化反应; (c) You 课题组报道的镍催化 C(sp^3)–H 键的芳基化反应

Figure 7 (a) Ni-catalyzed alkylation of C(sp^3)–H bonds by Ge group; (b) Ni-catalyzed arylation of C(sp^3)–H bonds by Chatani group; (c) Ni-catalyzed arylation of C(sp^3)–H bonds by You group

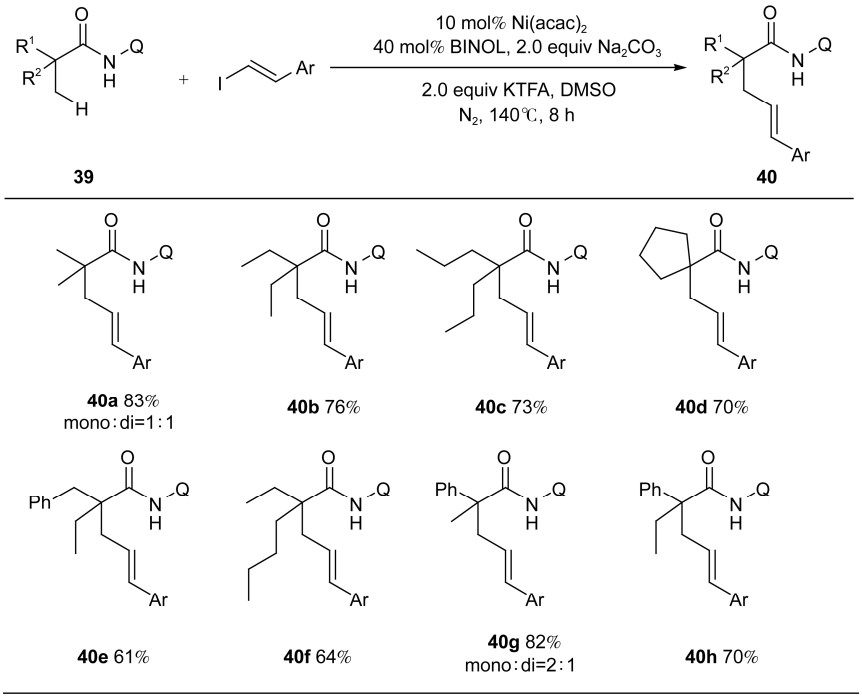

图 8 镍催化 C(sp^3)–H 键的烯基化反应

Figure 8 Ni-catalyzed alkenylation of C(sp^3)–H bonds

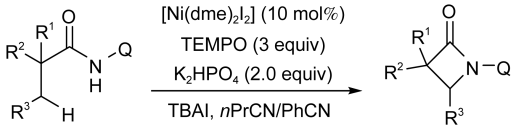

图 9 镍催化 C(sp^3)–H 键活化/分子内酰胺反应

Figure 9 Ni-catalyzed intramolecular amidation of C(sp^3)–H bonds

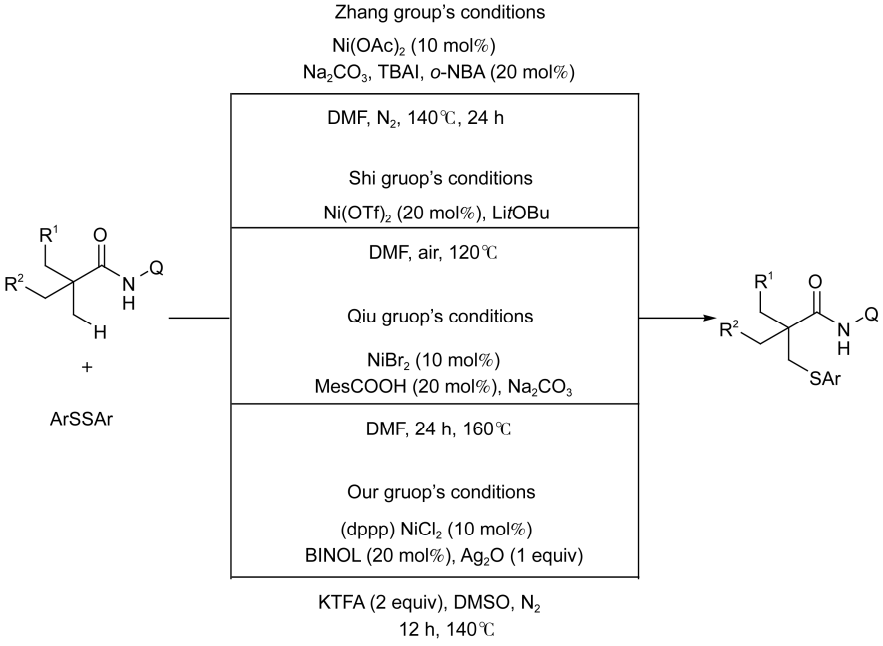

图 10 镍催化 C(sp^3)–H 键活化/C–S 键形成反应

Figure 10 Ni-catalyzed thilation of C(sp^3)–H bonds

3 结论

综上所述，由于镍在自然界的含量相对较为丰富，并且具有良好的催化活性，近年来有关镍催化的碳氢键活化反应屡有报道．但是仍有许多问题需要解决：(1) 目前镍催化的惰性碳氢键活化底物较为局限，反应主要局限在以双齿导向基辅助，其他类型导向基的应用较少，设计和发展新的导向基，以实现其他官能团导向的碳氢键活化反应具有极大的挑战性；(2) 镍催化的惰性碳氢键活化所需的反应温度都较高，如何设计新的催化体系降低反应温度也是一个很大的难题；(3) 目前镍催化的惰性碳氢键活化官能团化的反应类型较为局限，发展新的镍催化体系，用于构建各种碳杂键也是未来研究的重点领域；(4) 镍催化的惰性碳氢键活化的机理尚不明了，通过物理和化学等手段，对其机理进行深入理解，进而指导发展新反应，也是未来的研究方向之一．

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Recent progress on nickel-catalyzed direct functionalization of unactivated C–H bonds

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Over the past few decades, transition-metal catalyzed direct functionalization of unactivated C–H bonds has emerged as an efficient and straightforward strategy for the construction of C–C and C–heteroatom bonds. It provides access to complex molecules via the direct cleavage of C–H bonds without the need of prefunctionalization, rendering this strategy more step-economical and environmentally benign. Recently, tremendous attentions have been devoted to the use of first row-transition metals as most of those metals are naturally abundant, readily available, and inexpensive and have low toxicities in comparison with precious metals. In addition, the exploration of new catalytic systems might lead to the discovery of new mode of reactions. The aim of this review is to give an overview on recent advances in nickel-catalyzed direct functionalization of unactivated C–H bonds, without the discussion of the cleavage of acidic C–H bonds. Firstly, nickel-catalyzed functionalization of C(sp^2)–H to form new C–C and C–heteroatom bonds is reviewed. Secondly, an overview of Ni-catalyzed C(sp^3)–H functionalization is provided. In addition, mechanistic hypothesis and general aspects of these reactions have also been summarized. Finally, the limitations and perspectives on nickel-catalyzed C–H functionalization are discussed.

C–H activation, nickel, functionalization, inert

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