



丰产金属催化不对称还原 sp^3 - sp^3 偶联

何娇^{1,2}, 俞琼², 李玉龙^{1*}, 舒伟^{1,2*}

1. 四川轻化工大学化学与环境工程学院, 绿色催化四川省高校重点实验室, 自贡 643000

2. 南方科技大学深圳市格拉布斯研究院, 化学系, 广东省催化化学重点实验室, 深圳 518055

* 联系人, E-mail: yu_longli@suse.edu.cn; shuw@sustech.edu.cn

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摘要 饱和碳原子和杂原子手性中心(sp^3 杂化)是有机分子的主要组成结构单元, 广泛存在于天然产物、药物分子和功能材料等有机小分子和大分子中. 其中, 过渡金属催化的不对称 sp^3 - sp^3 偶联可以一步引入两个饱和原子中心(sp^3 杂化), 是构建分子饱和度的最高效方法之一. 传统的过渡金属催化的 sp^3 - sp^3 偶联方法主要依赖于预制备的当量有机金属试剂(如格氏试剂、有机锌、有机硼试剂、有机硅试剂等)与当量有机亲电试剂的交叉偶联反应. 然而这类方法通常需使用当量的预制备的有机金属试剂, 从而导致不对称 sp^3 - sp^3 偶联反应受到多种局限. 近年来, 丰产金属催化还原偶联策略使用低毒和储量丰富的丰产金属, 有助于饱和键的偶联成键; 同时, 还原偶联模式无需使用当量的有机亲核试剂, 为不对称 sp^3 - sp^3 偶联提供了新的机遇. 本综述系统总结了丰产金属催化还原不对称 sp^3 - sp^3 偶联的进展, 并进一步展望了该领域的未来发展方向.

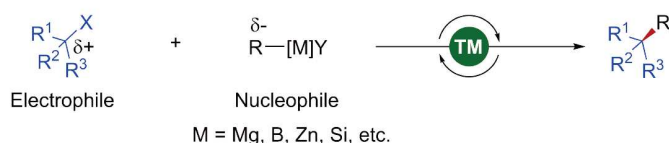
关键词 丰产金属催化, 还原偶联, 不对称偶联, sp^3 - sp^3 偶联, 饱和手性中心

饱和碳原子及杂原子手性中心是有机小分子的核心结构单元, 广泛存在于生物活性分子和功能材料^[1~3]. 在分子中引入饱和原子手性中心可以快速提高分子的饱和度, 增加分子的三维立体结构, 从而进一步影响分子的三维空间排列、理化性质、活性及功能等^[4~10]. 研究表明, 有机分子的成药性和分子的饱和度成正相关^[1,11]. 另外, 对映异构体之间往往表现出显著甚至截然不同的生物活性和光学性质等^[12,13]. 因此, 发展高效、高选择性的方法构建手性 sp^3 - sp^3 键(Csp^3 - Csp^3 及 Csp^3 -杂原子偶联等)是快速引入饱和手性中心的重要方法. 经过多年的发展, 已经发展出多种高效的构建手性 sp^3 - sp^3 键的方法. 催化不对称自由基加成、催化不对称自由基-自由基偶联和催化不对称 sp^3 - sp^3 偶联是构建手性 sp^3 - sp^3 键的三种有效的合成方法^[6,14~20]. 其中, 过渡金属催化的不对称 sp^3 - sp^3 偶联通过烷基金属中间体的

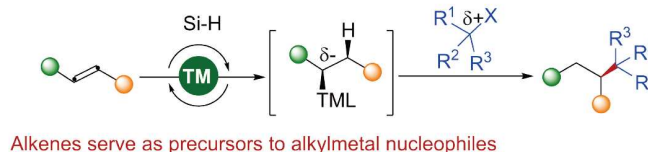
的还原消除形成手性 sp^3 - sp^3 键, 具有模块化等特点, 但同时具有存在中间体柔性大, 对映选择性控制困难等挑战. 另外, 由于多种 sp^3 杂化有机金属中间体的存在, 使得 β -氢消除等竞争性副反应多. 因此, 丰产金属在催化不对称 sp^3 - sp^3 偶联具有很大的优势. 传统的过渡金属催化不对称 sp^3 - sp^3 偶联依赖于使用预制的有机金属亲核试剂(如格氏试剂、有机锌试剂、有机硼试剂、有机硅试剂等)与烷基亲电试剂的不对称偶联(图1(a)). 其优点在于反应发展成熟、适用性广, 至多可构建两个连续手性中心^[8,21~24]. 然而, 该方法需使用当量的有机金属试剂, 需要提前预制备. 另外, 有机金属试剂来源有限, 其中部分有机金属试剂具有碱性强, 对空气和水敏感等缺点, 从而可能导致官能团兼容性、原子经济性和步骤经济性问题, 限制了其进一步广泛应用. 另一方面, 金属氢物种可对烯烃进行迁移插入, 选择性催

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He J, Yu Q, Li Y-L, et al. Abundant-metal catalyzed reductive asymmetric sp^3 - sp^3 coupling (in Chinese). Chin Sci Bull, doi: 10.1360/CSB-2025-5598

a) Traditional transition-metal-catalyzed asymmetric sp^3 - sp^3 cross-coupling reactions**Limitations:**

- Pre-preparation of stoichiometric organometallic nucleophiles
- Relative limitation of alkylmetal reagents
- High cost and time-consuming

b) Transition-metal-catalyzed asymmetric sp^3 - sp^3 cross-coupling reactions between alkenes and alkyl electrophiles**Advantages:**

- Avoidance of stoichiometric alkyl nucleophiles

Limitations:

- Dependence on the structural specificity of alkene substrates
- Use of excess silane

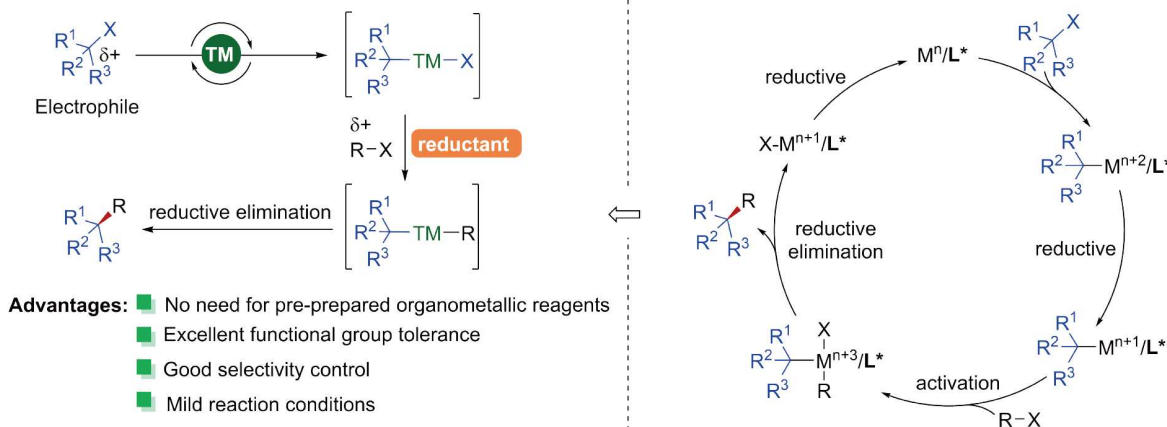
c) Earth-abundant metal-catalyzed asymmetric reductive sp^3 - sp^3 cross-coupling reactions

图1 (网络版彩色)过渡金属催化不对称 sp^3 - sp^3 键偶联策略。(a) 传统的过渡金属催化不对称 sp^3 - sp^3 交叉偶联反应。(b) 过渡金属催化烯烃与烷基亲电试剂的不对称 sp^3 - sp^3 交叉偶联反应。(c) 丰产金属催化不对称还原 sp^3 - sp^3 交叉偶联反应

Figure 1 (Color online) Strategies for transition-metal-catalyzed asymmetric sp^3 - sp^3 bond coupling. (a) Traditional transition-metal-catalyzed asymmetric sp^3 - sp^3 cross-coupling reactions. (b) Transition-metal-catalyzed asymmetric sp^3 - sp^3 cross-coupling reactions between alkenes and alkyl electrophiles. (c) Earth-abundant metal-catalyzed asymmetric reductive sp^3 - sp^3 cross-coupling reactions

化生成烷基金属物种^[9,25-31]。该物种进一步发生不对称 sp^3 - sp^3 偶联可以构建不对称烷基-烷基键、碳氮键等(图1b)。该策略使用烯烃作为烷基亲核试剂的前体,从而避免使用当量烷基亲核试剂。该策略不仅反应条件温和,且烯烃原料来源广泛,为构建结构更加多样性的不对称 sp^3 - sp^3 键提供了潜在可能。然而,该方法目前仍然依赖烯烃的取代模式和导向基团调控来实现氢金属的区域和立体选择性控制。同时该方法对多取代烯烃的实用性较低。

丰产金属催化还原偶联直接采用易得、稳定的有机亲电试剂作为反应底物,避免了传统方法中对空气敏感且原子经济性低的有机金属试剂的使用,极大提高了步骤经济性和官能团兼容性。另外,该类反应在还原条

件下进行,金属中心保持低价态,能有效抑制 β -氢消除等副反应,从而为实现 sp^3 - sp^3 键的构建提供了天然的优势。此外,该反应模式的官能团耐受性较好,并可结合电化学或光氧化还原等催化模式,进一步拓展了反应的化学空间。近十年来,丰产金属催化不对称 sp^2 - sp^3 还原偶联取得了巨大发展,已成为构建不对称 sp^2 - sp^3 键的主要方法之一。然而,与之相比,丰产金属催化不对称 sp^3 - sp^3 还原偶联仍然面临巨大挑战。该反应只需使用 sp^3 杂化的亲电试剂作为偶联前体显示出很好的发展潜力。近年来,丰产金属催化不对称 sp^3 - sp^3 还原偶联逐渐受到化学家的关注(图1(c))。本文从反应设计和发展、机理研究及合成应用等方面,系统综述该领域的最新进展,并对未来发展方向与待解决的关键问题进行展望。

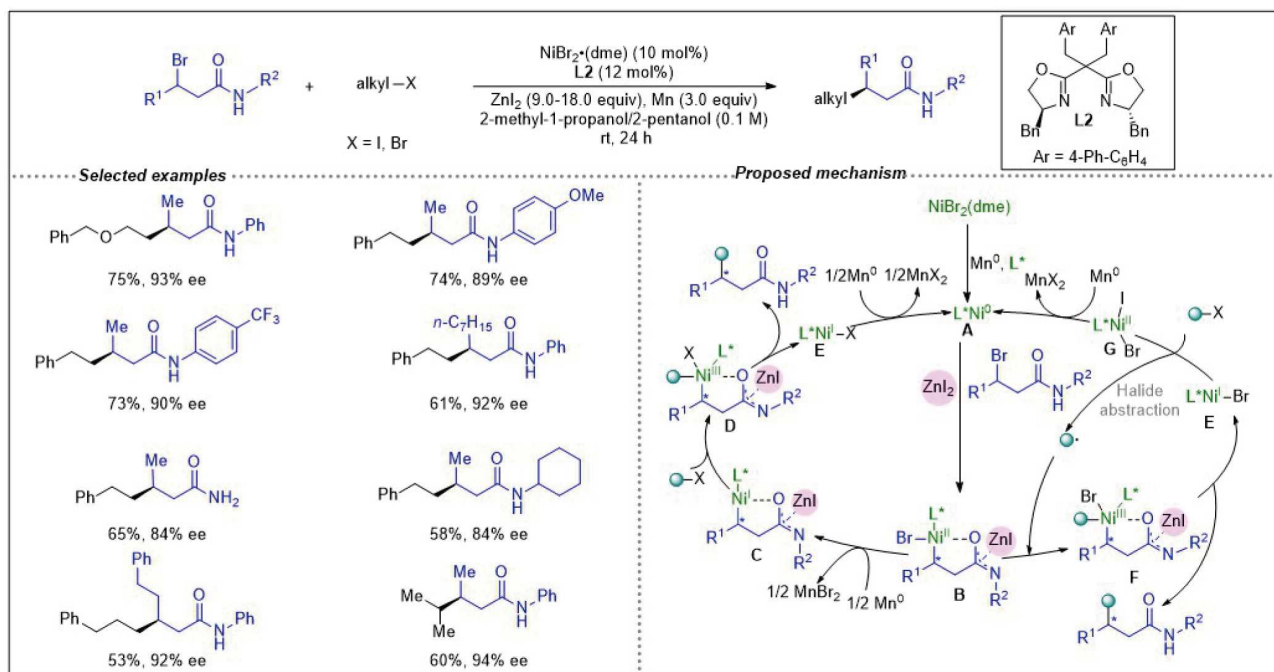


图3 (网络版彩色)镍催化非活化烷基卤代物的不对称还原交叉偶联

Figure 3 (Color online) Nickel-catalyzed asymmetric reductive cross-coupling between distinct unactivated alkyl halides

待进一步研究。机理研究表明, 锰粉首先将 $Ni(II)$ 还原为 $Ni(0)$ 物种(A), 随后在碘化锌(ZnI_2)存在下, A与 β -溴代酰胺发生氧化加成, 生成烷基 $Ni(II)$ 中间体(B)。该中间体被锰单电子还原为烷基 $Ni(I)$ 物种(C)。C与另一组分非活化烷基卤代物发生氧化加成, 生成二烷基 $Ni(III)$ 中间体(D)。该中间体经还原消除生成目标产物并再生 $Ni(I)$ 物种(E), E经单电子还原再生 $Ni(0)$ 物种(A), 完成催化循环。此外, 研究指出反应可能存在另一种反应路径: $Ni(I)$ 物种(E)与非活化烷基卤代物发生单电子氧化加成, 生成二价镍中间体G和烷基自由基。烷基自由基与烷基 $Ni(II)$ 中间体(B)结合形成二烷基 $Ni(III)$ 中间体(F), 后者经还原消除同样得到目标产物。 ZnI_2 对反应具有重要作用, 可能通过与酰胺基团配位形成稳定复合物, 增强反应活性和选择性控制。该反应首次实现了镍催化还原条件下的烷基-烷基不对称偶联, 为不对称烷基-烷基偶联提供了新的反应模式。

2024年, 刘文斌课题组报道了镍催化氮杂环丙烷与烷基溴代物的不对称还原开环烷基化反应^[36]。如图4所示, 该反应以 $NiCl_2 \cdot (dme)$ 为催化剂, 锰粉为还原剂, 在手性吡啶-咪唑啉配体L3的调控下, 成功实现了外消旋N-磺酰基苯乙炔基氮杂环丙烷与一级烷基溴化物的不对称还原交叉烷基-烷基偶联, 高效构建了含 β -手性

叔碳中心的苯乙胺类衍生物。该反应具有优异的区域选择性和良好的官能团兼容性。一系列一级烷基溴化物(包括直链及含卤原子、缩醛、醛、酯、醚、硼酸酯等官能团修饰的底物)均可顺利参与该反应。美中不足的是, 该反应体系对二级及三级烷基溴代物尚未表现出反应活性, 此类底物的适用性仍有待进一步优化。另外, 多种N-磺酰基苯乙炔基氮杂环丙烷均适用于该反应, 以中等至优良收率及优异的对映选择性得到相应开环产物。机理研究表明, 氮杂环丙烷首先在反应体系中经历区域选择性开环碘解, 生成苄基碘中间体A'。随后, 该中间体与 $Ni(I)Br$ 物种经过卤原子转移发生单电子氧化加成, 生成苄基自由基A与 $Ni(II)$ 物种。苄基自由基与 $Ni(II)$ 物种发生对映选择性结合, 形成手性苄基 $Ni(III)$ 中间体B。该步骤为该反应的对映选择性决定步骤。中间体B被锰还原为手性苄基 $Ni(I)$ 中间体C。该中间体与一级烷基卤代物经单电子氧化加成生成新的 $Ni(III)$ 中间体D。该中间体最终经还原消除生成目标产物并再生 $Ni(I)Br$ 物种, 完成催化循环。该方法首次实现了镍催化下氮杂环丙烷与烷基溴代物之间的还原不对称交叉偶联, 为 β -手性苯乙胺类化合物的合成提供了一条高效、高选择性的途径。

2024年, 陈良安课题组报道了镍催化烯烃与芳基

Figure 4 (Color online) Nickel-catalyzed ring-opening asymmetric sp^3 - sp^3 reductive cross-coupling reaction between aziridines and alkyl halides

最近, 黄渊、刘松等人报道了一种镍催化 β -氨基醇磺酸酯与烷基亲电试剂的对映选择性迁移还原交叉偶联反应, 高效合成了一系列 β -烷基取代的 β -苯乙胺衍生物^[38]。该反应经历自由基1,2-氨基迁移过程。该反应以 $\text{NiCl}_2 \cdot (\text{dme})$ 为催化剂, 锰粉为还原剂, 在手性双咪唑啉

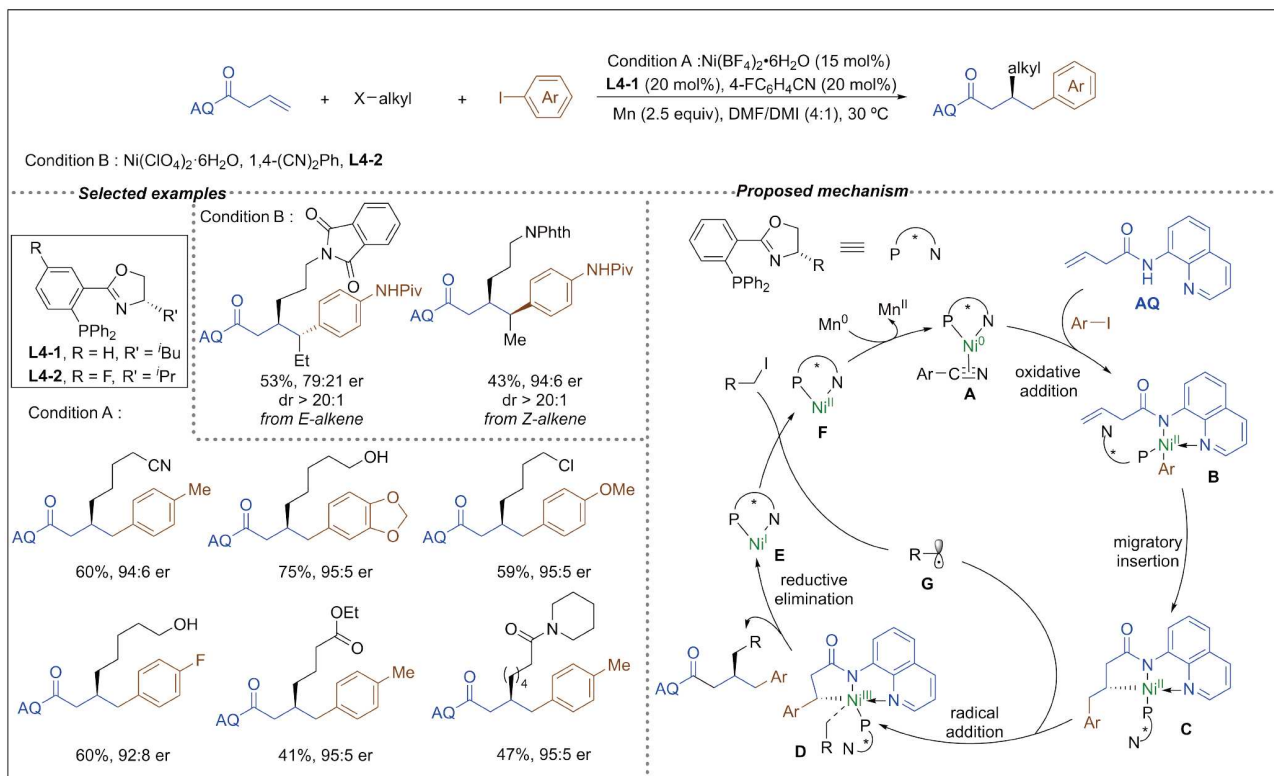


图5 (网络版彩色)镍催化三组分烯烃不对称还原芳基烷基化反应

Figure 5 (Color online) Nickel-catalyzed three-component asymmetric reductive arylalkylation of alkenes

配体L5调控下, 成功实现了 β -苯基氨基醇磺酸酯与烷基亲电试剂的不对称迁移交叉偶联, 高效构建了一系列结构多样的手性 β -烷基取代的 β -苯乙胺衍生物(图6)。该策略具有优异的底物普适性和官能团兼容性。苯环上连有烷基、烷氧基、卤素等不同取代基的N-磺酰基 β -氨基醇衍生物均可顺利参与反应。另外, 不同长度的直链和含有氟、氯、三氟甲基、酯基、醚键、硅醚、烯烃、苯基、萘基、杂芳环等官能团的烷基亲电试剂在该体系中均得到很好的兼容。遗憾的是, 该反应不适用于二级和三级烷基亲电试剂。机理研究表明, 反应经历烷基磺酸酯与碘化物交换、Ni-C键均裂以及自由基1,2-氨基迁移等关键步骤。锰粉首先将Ni(II)催化剂还原为Ni(0)物种(A)。NaI与 β -苯基氨基醇磺酸酯发生碘离子交换生成相应的烷基碘化物。该烷基碘化物与Ni(0)物种(A)发生氧化加成得到烷基Ni(II)中间体(B)。该中间体被锰还原为烷基Ni(I)物种(C)。C与第二分子的一级烷基亲电试剂经单电子氧化生成Ni(III)物种(D), 并进一步发生选择性Ni-C键均裂, 形成 α -胺基烷基自由基Ni(II)中间体(E)。E通过分子内1,2-氨基迁移生成

更稳定的苄基自由基(F)。F与Ni(II)物种E结合生成Ni(III)-苄基中间体(G)。G经还原消除得到目标产物和Ni(I)物种(H)。H经锰还原重生Ni(0)物种(A)完成催化循环。

2 电化学介导镍催化不对称烷基-烷基偶联

电化学介导的还原体系通过电子转移驱动反应, 符合绿色合成理念^[39]。尽管电化学条件下的双重脱羧交叉偶联已被证实可用于高效构建C(sp³)-C(sp³)键, 但其对映选择性控制长期以来未能取得突破性进展^[40,41]。2023年, Baran课题组报道了首例底物控制的对映选择性双脱羧烷基-烷基交叉偶联反应(dDCC)^[42]。在镍催化与电化学反应条件下, 可以实现两个羧酸氧化还原活性酯(NHPI redox active esters)的双脱羧偶联, 高对映选择性生成具有 α -烷基化手性中心的酰胺衍生物。如图7所示, 该体系以NiCl₂·(dme)为催化剂, 新型三齿配体L6为关键配体, Mg阳极和网状玻璃碳(reticulated vitreous carbon, RVC)电极为阴极的电化学体系中(含MgBr₂、FeBr₃添加剂及LiBr电解质), 成功实现烷基羧

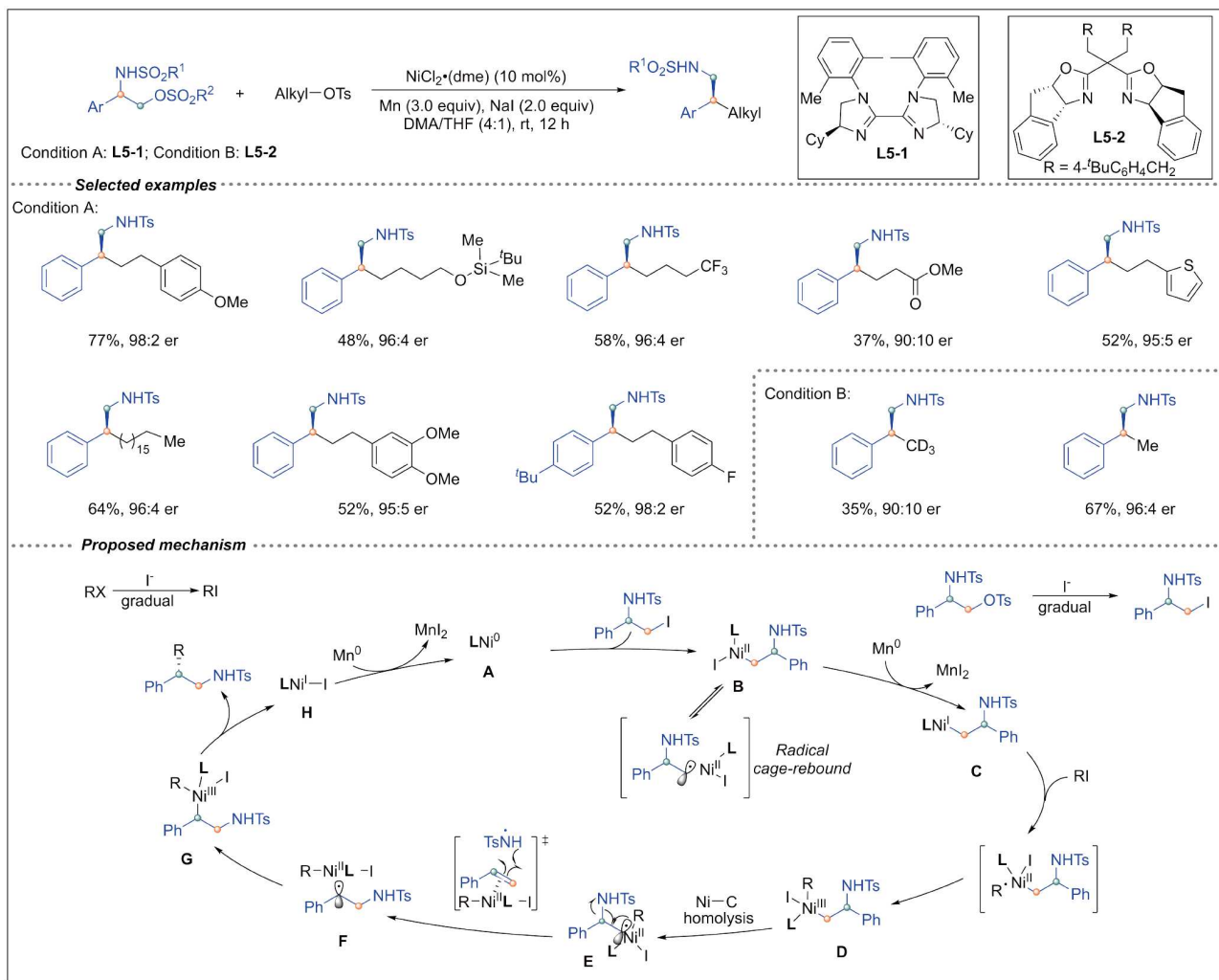


图6 (网络版彩色)镍催化1,2-氨基转移不对称还原烷基-烷基偶联反应

Figure 6 (Color online) Nickel-catalyzed 1,2-amino transfer asymmetric reductive alkyl-alkyl coupling reaction

酸衍生物和丙二酸半酰胺衍生物之间的对映和非对映选择性双重脱羧交叉偶联反应。该反应底物普适性优异,含末端/内烯炔、末端/内炔炔、三氟甲基、烷基卤、芳基卤、酮、醚、酯、杂环(噻吩、呋喃)等官能团的一级烷基羧酸衍生物,均可顺利反应。同时,丙二酸半酰胺化合物其结构可以涵盖带给电子或吸电子取代的苯环,以及烷基氟化物、腈、内炔等,均能顺利发生不对称交叉偶联,得到相应的不对称偶联产物。即使底物中已存在手性中心,反应仍能高非对映选择性构建目标产物。然而,该反应对二级烷基羧酸衍生物不兼容。对于丙二酸半酰胺衍生物,三级芳基酰胺、二级脂肪族酰胺及酯类,均不发生有效反应。尽管该反应体系的机制尚不明确,但通过类比先前研究结果,推测可能

机理是:首先,在电化学条件下, Ni(II)被还原为具有催化活性的低价镍物种(如Ni(I)或Ni(0))。低价镍可还原烷基羧酸衍生物和丙二酸半酰胺衍生物以产生烷基自由基,同时烷基羧酸衍生物和丙二酸半酰胺衍生物也可能通过直接阴极还原生成烷基自由基。接着,生成的两种不同烷基自由基会依次与低价镍活性物种结合形成 Ni-C键中间体,此过程中镍的氧化态会通过化学途径(歧化或归中反应)或电化学途径进行调节。最后,两种 Ni-C键中间体发生还原消除反应,形成新的 sp³-sp³键,同时释放出低价镍物种以完成催化循环。非线性效应研究表明活性催化物种为含单个手性配体的单体 Ni 配合物,这为中间体的选择性形成提供了依据。

2025年, Baran团队开发并报道了一种新型镍/电催

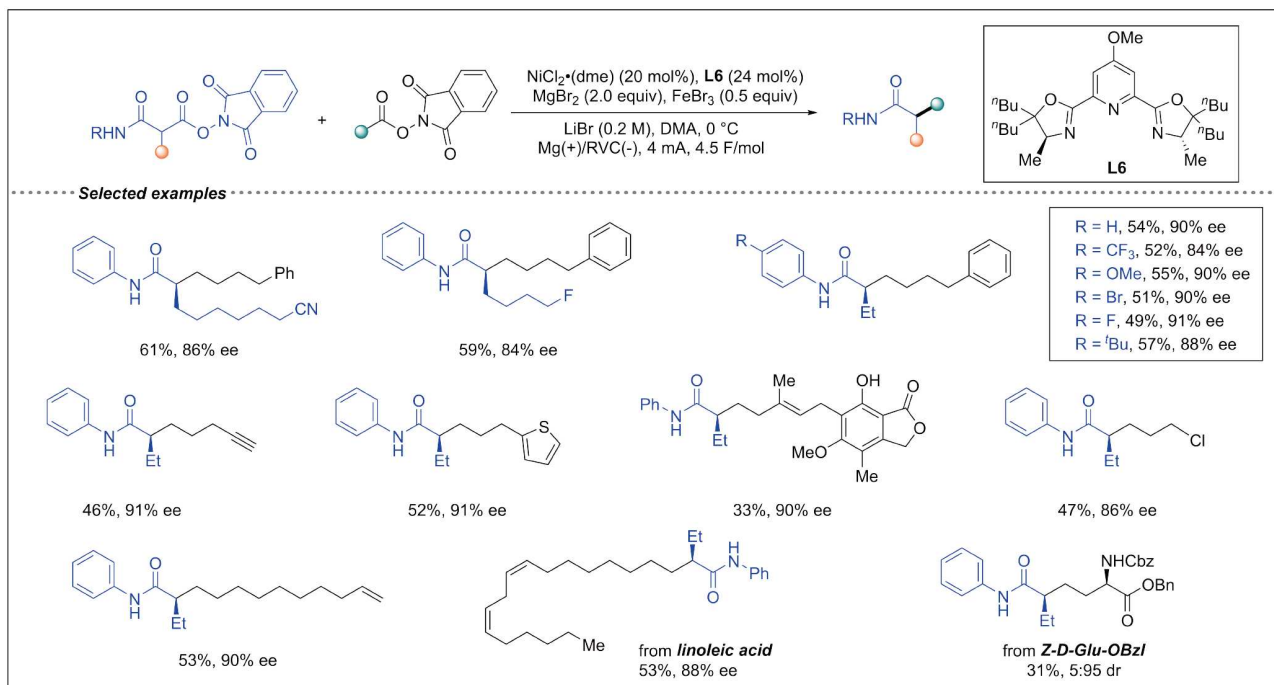


图7 (网络版彩色) 电化学介导镍催化双重脱羧不对称还原烷基-烷基交叉偶联

Figure 7 (Color online) Electrochemically mediated nickel-catalyzed dual-decarboxylative asymmetric reductive alkyl-alkyl cross-coupling

化脱羧自由基交叉偶联体系^[43]。如图8所示,在该体系中,以NiCl₂·(dme)为催化剂,2,6-双(吡嗪基)吡啶(bpp)为配体,结合Mg阳极/RVC阴极的电解条件,能够实现丝氨酸衍生的手性氧化还原活性酯与烷基羧酸氧化还原活性酯/苄基卤化物发生脱羧偶联反应,获得具有单一构型(dr>20:1)的1,2-氨基醇。该反应体系具有优异的底物普适性,含硅醚、酯基、烯基、三氟甲基、氨基甲酸酯基、酮羰基等多种官能团的链状一级烷基羧酸氧化还原活性酯,以及四至六元环状和非环状的二级烷基羧酸氧化还原活性酯,均可顺利参与反应。遗憾的是,使用不对称二级烷基羧酸氧化还原活性酯时,获得的产物为非对映异构体混合物,未能实现单一非对映体选择性控制。同时,含给电子/吸电子基团的多取代苄基溴和三氮唑基溴化物等可顺利发生脱羧苄基化反应,且苄基溴的偶联产物纯度高于对应烷基羧酸氧化还原活性酯的产物。通过非线性效应研究、循环伏安研究及前期研究成果,对该反应机理进行了推测。首先,在电化学条件下,Ni(II)经阴极还原生成低价镍活性物种,并与配体结合形成低价镍中间体。接着,丝氨酸衍生的手性氧化还原活性酯与低价镍中间体通过单电子转移断裂C-O键生成自由基,丝氨酸衍生的手性氧化还原活性酯的刚性双环骨架限制自由基旋转以保障

后续立体控制。其中,部分丝氨酸衍生的手性氧化还原活性酯也可能通过直接阴极还原辅助生成自由基。随后,两种自由基依次与Ni中心结合形成双Ni-C键中间。最后,中间体经还原消除形成目标化合物。

3 光介导镍催化不对称烷基-烷基偶联

2023年,徐涛课题组利用光/镍协同催化策略,实现了消旋 α -氯代硼酸酯与未活化烷基碘化物的对映汇聚性还原交叉烷基-烷基偶联反应^[44]。如图9所示,该反应以NiBr₂·(dme)为催化剂,汉茨希酯(Hantzsch酯, HEH)为还原剂,2,4,5,6-四(9-呋唑基)-间苯二腈(4CzIPN)为光催化剂,在30 W蓝光发光二极管(light-emitting diode, LED, 450~455 nm)照射和新型手性双噁唑啉配L7存在下,合成了一系列手性二级烷基硼酸酯化合物。该反应体系的底物普适性优异且全面:多种一级烷基碘化物均能顺利参与反应,对酯基、醚、氰基、三氟甲基、酰胺、烷基氯化物、酚羟基、酮,以及多种天然产物衍生物等均展现出良好兼容性。此外,二级烷基碘化物也可用于合成具有高对映选择性的手性硼酸酯,但三级烷基碘因空间位阻大无法参与反应。 α -氯硼酸酯在反应中表现出良好的反应活性,能够耐受烷基氯、醚、酯、醇、烯烃等官能团,所得产物产率中等至良好,且

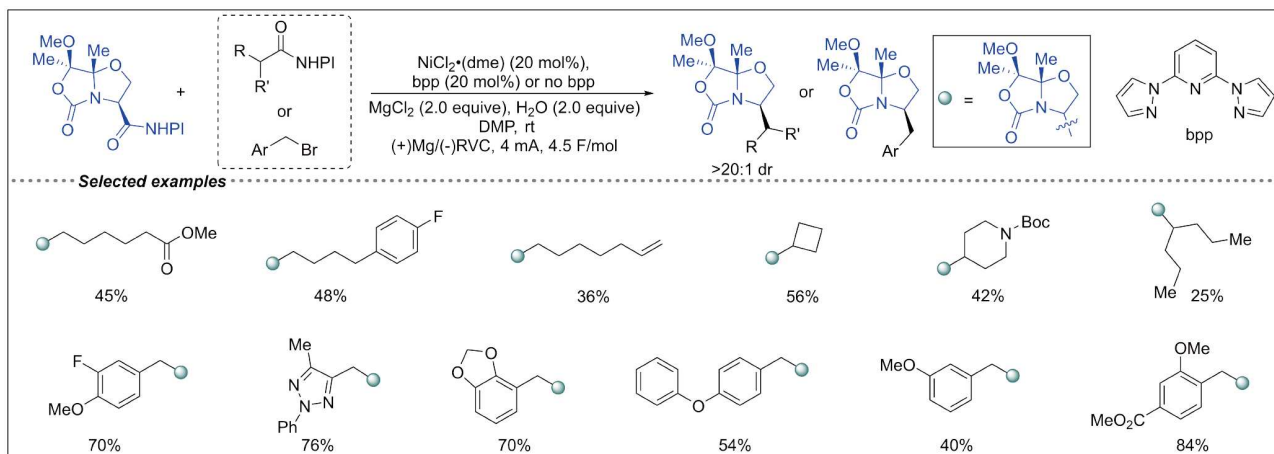


图8 (网络版彩色) 电化学介导镍催化烷基-烷基还原偶联实现氨基醇衍生物的立体选择性合成

Figure 8 (Color online) Electrochemically mediated nickel-catalyzed alkyl-alkyl reductive coupling for the stereoselective synthesis of amino alcohol derivatives

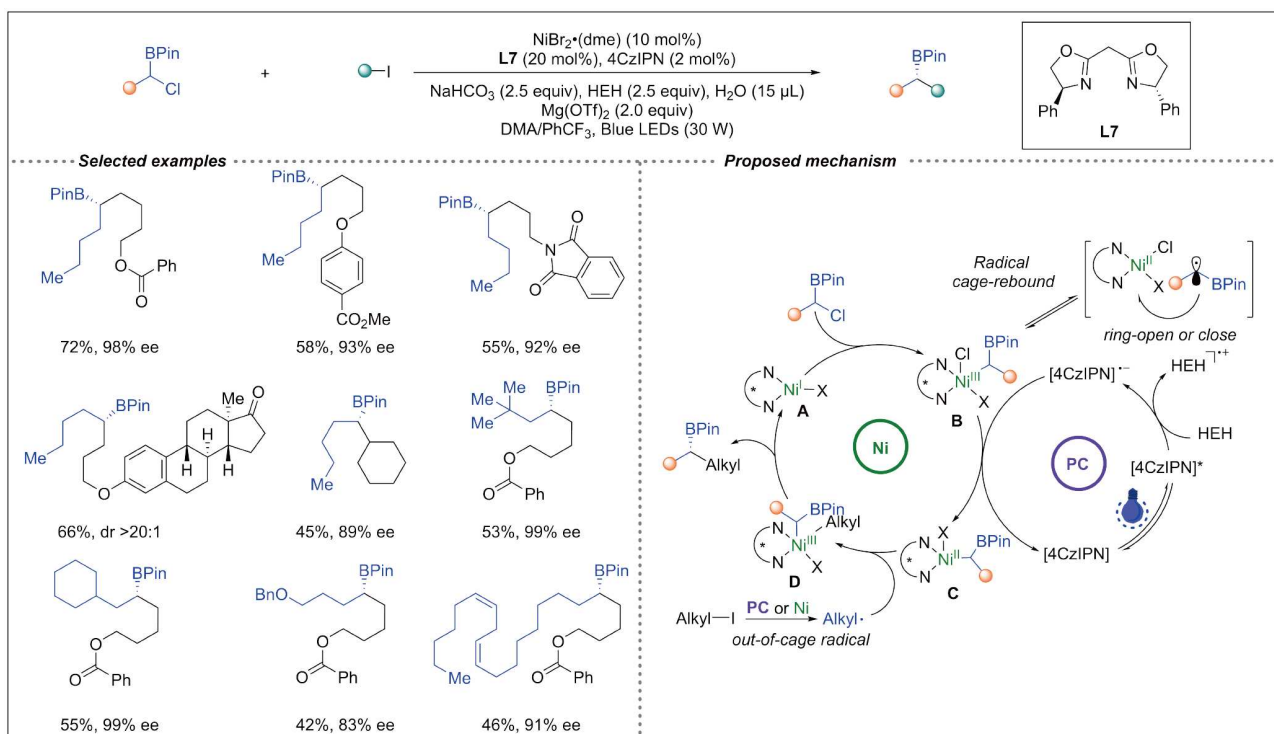


图9 (网络版彩色) 光/镍协同催化不对称还原交叉烷基-烷基偶联

Figure 9 (Color online) Photo/nickel dual catalyzed asymmetric reductive cross alkyl-alkyl coupling

对映选择性较高。然而, 具有高度空间位阻的 β,β -二取代 α -氯代硼酸酯则难以顺利反应。机理研究表明, α -氯代硼酸酯与Ni(I)物种(A)发生氧化加成反应, 生成Ni(III)中间体(B), 且该中间体B能够与自由基钟底物发生开环/闭环反应。B经光氧化还原体系进行还原后, 形成Ni(II)中间体(C)。C会被由烷基碘生成的烷基自由基

氧化, 从而生成Ni(III)中间体(D)。最后, D发生还原消除得到手性二级烷基硼酸酯目标化合物, 并再生Ni(I)物种(A), 完成催化循环。

2025年, 杨泽鹏课题组报道了一种镍/光协同催化体系, 可实现 β -羟基酰胺和烷基N-羟基邻苯二甲酰亚胺酯(NHP)的对映选择性自由基-自由基交叉偶联反

应^[45]. 如图10所示, 该反应以 $\text{NiBr}_2 \cdot (\text{dme})$ 为催化剂, 二[2-(2,4-二氟苯基)-5-三氟甲基吡啶][2-2'-联吡啶]铱二(六氟磷酸)盐 $\{[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6\}$ 为光催化

剂, 辅以氮-杂环卡宾(NHC)和新型手性二胺配体 L8 , 并在30 W蓝光LED(455 nm)照射下, 成功合成出一系列含手性叔碳中心化合物. 该反应展现出优异的底物普适

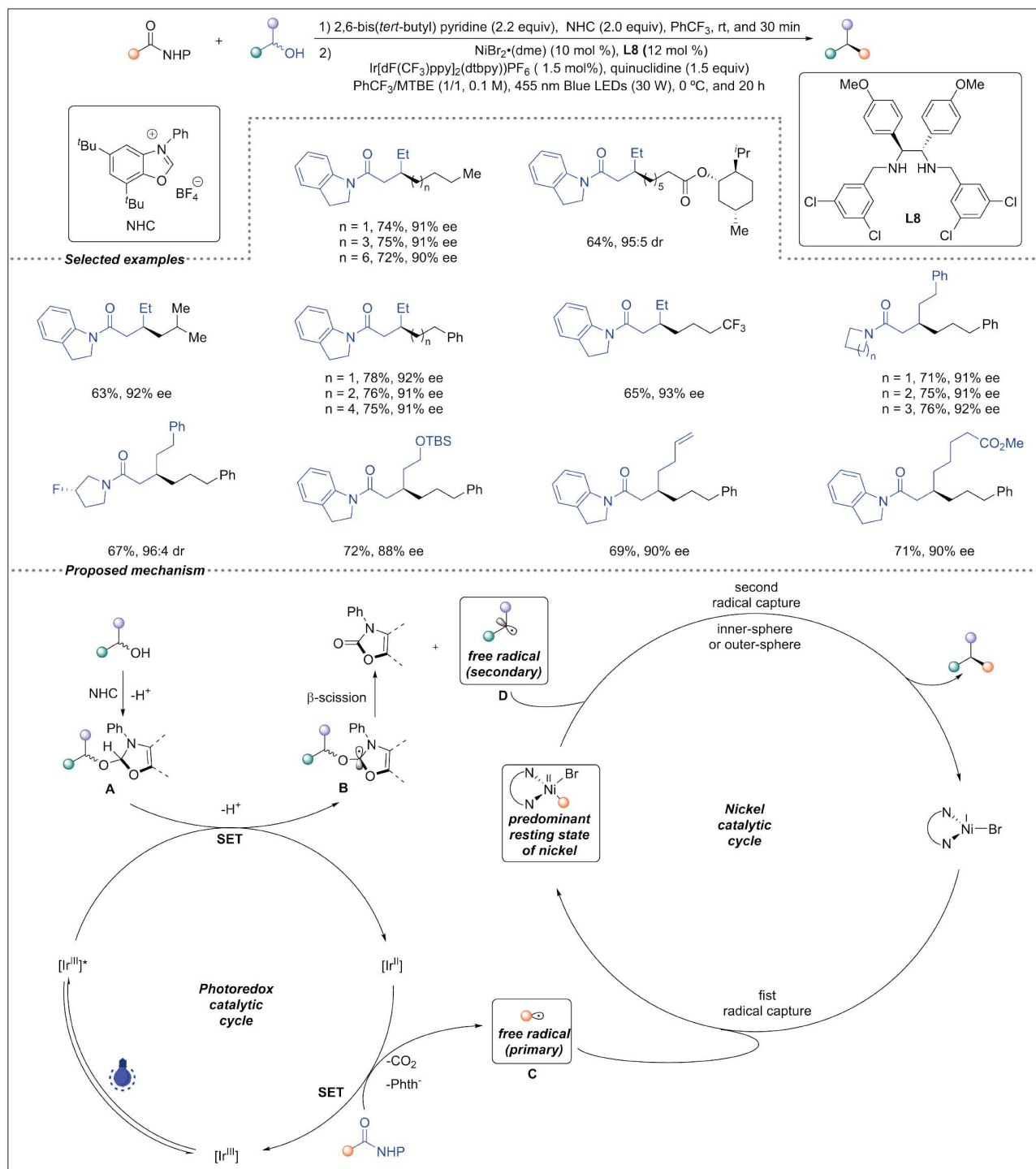


图10 (网络版彩色)光/镍协同催化 β -羟基酰胺和 N -羟基苯酞亚胺酯的不对称还原烷基-烷基偶联

Figure 10 (Color online) Photo/nickel dual-catalyzed asymmetric reductive alkyl-alkyl coupling between β -hydroxyamides and N -hydroxyphthalimide esters

β -H消除生成烯烃配位的钴中间体(E), 再经烯烃插入Co-H键形成烷基钴中间体(F). 最后, 中间体F与HBpin通过 σ 键复分解或氧化加成-还原消除生成目标硼酸酯和Co-H物种(G). 利用Co(salen)配合物与手性配体L9的协同作用, 外消旋烷基溴化物可通过对映选择性自由基路径, 生成高ee值的手性苄基硼酸酯.

5 总结与展望

近年来, 丰产金属催化不对称还原 sp^3 - sp^3 偶联反应取得了显著进展. 其中, 镍催化体系成功实现了烷基卤化物、氧化还原活性酯等底物的对映汇聚式还原偶联. 该还原偶联策略成功规避了传统方法中需预制备烷基金属试剂的局限, 显著提升了反应的效率与官能团兼容性, 为不对称 sp^3 - sp^3 键的构建提供了高效、绿色的合成新途径. 尽管该领域已取得突破性进展, 但是该领域仍然处于发展初期, 面临诸多挑战. 首先, 目前仅实现了还原不对称烷基-烷基偶联和不对称烷基-硼偶联, 其他类型不对称还原 sp^3 - sp^3 偶联仍有待发展. 其次, 催化金属种类较为单一, 只有镍和钴被成功应用于不对称还原 sp^3 - sp^3 偶联, 其他丰产金属催化的不对称还原 sp^3 - sp^3 偶联反应尚未充分开发. 另外, 现有反应的底物

范围和应用场景仍然相对有限, 制约了其合成应用. 因此, 该领域仍然蕴藏广阔的发展机遇和挑战. 其一, 拓展底物普适性, 重点实现大位阻(如二级/三级烷基底物)、复杂结构 sp^3 亲电前体(如含多官能团或手性中心的底物)的高效不对称还原 sp^3 - sp^3 偶联, 以满足更广泛的合成需求; 其二, 深化反应机理研究, 借助原位光谱(如原位X射线光电子能谱、原位核磁共振)、电化学测试(如循环伏安法)及密度泛函理论(DFT)计算等手段, 明确催化体系中镍等金属活性物种的转化路径及手性配体的立体诱导机制, 为反应设计与优化提供理论支撑; 其三, 优化立体选择性调控策略, 积极开发新型手性配体以提升反应的对映选择性, 推动反应的精准化控制; 其四, 开发经济环保的非金属还原剂替代金属还原剂(锌、锰等), 促进光、电等绿色还原方式与丰产金属催化体系的融合, 降低对化学还原剂的依赖, 契合绿色化学的发展理念. 其五, 发展铜、铁、钴等其他丰产金属催化体系, 发掘其在还原不对称 sp^3 - sp^3 偶联中的独特潜力. 此外, 发展其他催化模式和协同催化模式等在丰产金属催化不对称还原 sp^3 - sp^3 偶联反应中的应用, 有助于推动不对称 sp^3 - sp^3 偶联反应的快速发展和应用.

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Summary for “丰产金属催化不对称还原 $\text{sp}^3\text{-sp}^3$ 偶联”

Abundant-metal catalyzed reductive asymmetric $\text{sp}^3\text{-sp}^3$ coupling

Jiao He^{1,2}, Qiong Yu², Yu-Long Li^{1*} & Wei Shu^{1,2*}

¹ College of Chemistry and Environmental Engineering, Key Laboratory of Green Catalysis of Higher Education Institutes of Sichuan, Sichuan University of Science and Engineering, Zigong 643000, China

² Shenzhen Grubbs Institute, Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China

* Corresponding authors, E-mail: yu_longli@suse.edu.cn; shuw@sustech.edu.cn

Saturated carbon and heteroatom stereogenic centers with sp^3 -hybridization are ubiquitous structural units in bioactive molecules, natural products, and functional materials. Introducing saturated stereogenic centers into molecules can rapidly increase molecular saturation, thus enhancing the three-dimensional structure of molecules and further affecting their spatial arrangement, physicochemical properties, activity, and functions. Studies have shown that the drug-likeness of organic molecules is positively correlated with their saturation. Therefore, developing efficient and highly selective methods to construct chiral $\text{sp}^3\text{-sp}^3$ bonds is a key approach for rapidly introducing saturated stereogenic centers. Among existing protocols, transition metal-catalyzed asymmetric $\text{sp}^3\text{-sp}^3$ cross-coupling forms asymmetric $\text{sp}^3\text{-sp}^3$ bonds through reductive elimination of organometallic intermediates. This reaction mode is characterized by modularity but also faces challenges, including the flexibility of intermediates, decreased rate of cross-coupling, and difficulties in controlling chemo- and enantioselectivity. In addition, the presence of multiple sp^3 -hybridized organometallic intermediates leads to many competitive side reactions, including β -hydride elimination. Therefore, abundant transition metals have significant advantages in catalyzing asymmetric $\text{sp}^3\text{-sp}^3$ cross-coupling over late transition metals. Over the past decades, abundant transition-metal-catalyzed asymmetric $\text{sp}^3\text{-sp}^3$ cross-couplings have achieved great progress. However, traditional abundant-transition-metal-catalyzed asymmetric $\text{sp}^3\text{-sp}^3$ coupling reaction heavily relies on the use of pre-synthesized organometallic nucleophiles (such as Grignard reagents, organozinc reagents, organoboron reagents, organosilicon reagents, etc.) to cross-couple with sp^3 -hybridized electrophiles. Organometallic reagents are limited in availability and suffer from high cost and sensitivity to air and/or moisture, potentially leading to issues with functional group compatibility, atom economy, and step economy, thus limiting their further application. On the other hand, reductive $\text{sp}^3\text{-sp}^3$ cross-coupling catalyzed by abundant-transition metals directly uses readily-available and bench-stable sp^3 -hybridized organic electrophiles as the sole coupling precursors, avoiding the use of air-sensitive and atom-inefficient organometallic reagents in traditional methods and significantly improving step economy and functional group compatibility. In addition, these reactions are carried out under reductive conditions by maintaining the transition-metal centers at low oxidation state, which could effectively suppress side reactions such as β -hydride elimination, favoring the formation of $\text{sp}^3\text{-sp}^3$ bonds. Furthermore, this reaction mode demonstrates good functional group tolerance and can be combined with electrochemical or photoredox catalysis to further expand the chemical space for organic synthesis and related areas. Over the past decade, abundant-transition-metal-catalyzed asymmetric $\text{sp}^2\text{-sp}^3$ reductive coupling has attracted more and more attention from synthetic chemists and has made significant progress, and is becoming one of the major options for constructing asymmetric $\text{sp}^2\text{-sp}^3$ bonds. This review systematically summarizes the development and progress in this field from the perspectives of reaction design and development, mechanistic studies, and synthetic applications. Catalytic asymmetric reductive alkyl-alkyl cross-coupling with different scenarios has been achieved using Ni-catalysis, photoredox and Ni-catalysis, as well electrochemical Ni-catalysis. Co-catalyzed asymmetric reductive alkyl-boron cross-coupling has also been initiated. However, the scope for asymmetric $\text{sp}^3\text{-sp}^3$ reductive cross-coupling catalyzed by abundant metals is very limited and still faces significant challenges. Accordingly, future directions for key challenges that need to be addressed in abundant-transition metal-catalyzed reductive asymmetric $\text{sp}^3\text{-sp}^3$ cross-coupling are also discussed.

earth-abundant-metal catalysis, reductive coupling, asymmetric coupling, $\text{sp}^3\text{-sp}^3$ coupling, saturated stereogenic center

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