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钯催化的烯烃与三嗪烷氢胺羰基化反应研究

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摘要: 酰胺类化合物广泛应用于医药、农药、材料、合成化学等领域, 因此, 新型且高效合成酰胺的方法一直具有很高的关注度. 我们首次使用环状脂肪三级胺类化合物—1,3,5-三嗪烷作胺源, 成功解决了钯催化的烯烃氢胺羰基化反应领域中脂肪胺对钯催化剂的毒化问题, 合成了多种烷基支链酰胺化合物, 并提出了可能的反应机理.

关键词: 钯催化; 烯烃; 1,3,5-三嗪烷; 氢胺羰基化; 烷基支链酰胺

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含酰胺结构的化合物广泛应用于天然产物、医药、农药、材料以及化工等领域 (图 1)[1−6]. 近几十年来, 研究并建立高效构建酰胺官能团的方法受到了合成化学家们的高度关注. 在众多合成酰胺化合物的方法中[7−11], 利用钯作催化剂, 通过反应过程中形成的钯-负氢活性物种, 完成烯烃氢胺羰基化反应, 从而实现酰胺化合物的合成, 是简易且高效的方法之一[12−21].

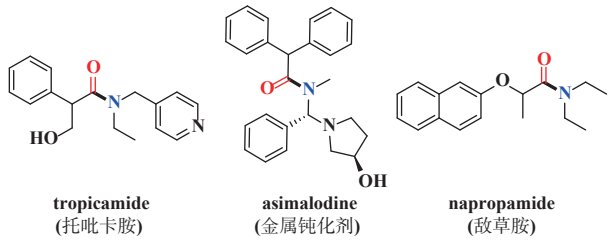

图 1　含酰胺结构的化合物示例

Fig.1 Examples for amide-containing compounds

自 2013 年 Beller 团队[22] 首次建立钯作催化剂, 芳香胺作胺源的烯烃氢胺羰基化反应以来 (图 2(a)), Beller[22−24]、Huang[25−29]、Liu[30]、Xu[31] 等研究小组相继利用不同的催化机理路径, 使用多种胺源, 极大拓展了烯烃氢胺羰基化反应的应用范围. 除芳香胺外, 烯烃的氢胺羰基化反应常见的胺源还包括硝基芳烃、酰胺、铵盐、盐酸羟胺以及胺缩醛等. 例如, 2015 年, Beller 团队[24] 以酰胺作胺源和亲核试剂, 成功实现了钯催化的烯烃氢胺羰基化反应, 合成出多种酰亚胺类化合物; 同样以酰胺为胺源, Huang 课题组[27] 利用配体调控的策略, 建立了一种高效的钯催化氢胺羰基化反应, 得到了直链酰胺和支链类酰胺产物; Huang 团队[28] 还以氯化铵作氨气的替代物, 实现了钯催化烯烃的氢胺羰基化反应, 选择性地合成出了直链和支链伯酰胺类化合物, 氯化铵同时也为钯-负氢物种提供了酸性环境; 此外, 他们[29] 利用盐酸羟胺作胺源, 建立了烯烃氢胺羰基化反应.

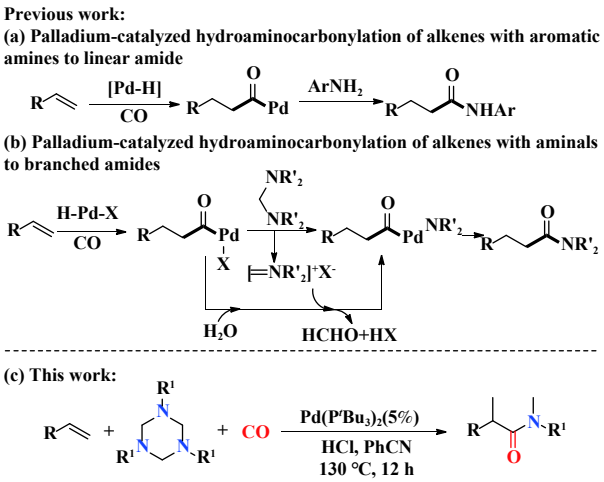

图 2　钯催化的氢胺羰基化反应

Fig.2 Palladium-catalyzed hydroaminocarbonylation

然而, 采用脂肪胺类化合物作胺源, 实现钯催化的氢胺羰基化反应的研究较为少见. 原因在于脂肪

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胺对催化活性中间体—钯-负氢有较强的毒化作用, 可抑制氢胺羰基化反应的发生. 为了克服这一难题, Huang 课题组[25] 采用链状胺缩醛作脂肪胺替代物, 有效避免了脂肪胺对钯-负氢物种的毒化, 实现了钯催化的烯烃氢胺羰基化反应 (图 2(b)). 我们首次采用环状脂肪三级胺类化合物—1,3,5-三嗪烷作胺源用于钯催化的氢胺羰基化反应, 成功解决了脂肪胺对催化剂的毒化问题, 合成出多种酰胺化合物 (图 2(c)).

1 实验部分

1.1 试剂和分析方法

实验中所使用的钯催化剂、膦配体、烯烃、胺类化合物和多聚甲醛均通过市售渠道购买; 反应所用溶剂通过安耐吉或百灵威试剂订购平台购买; ^{1}H NMR 和 ^{13}C NMR 光谱通过 BRUKER AvanceIII (400 MHz) 型核磁共振谱仪 (德国 Bruker 公司) 测定, 以氘代氯仿为溶剂, 非对映异构体 dr 值通过氢谱测定; 气相色谱使用安捷伦 7890B 进行分析, 色谱柱为 Hp-5, 以正十六烷为内标测定气相收率; GC-MS 使用安捷伦 7890B/5975B 进行分析; 硅胶 HSGF254 薄层板和柱色谱分离用硅胶 (粒径 0.050 ~0.071 mm) 购买于北京建强伟业科技有限公司; 柱色谱分离用淋洗剂为市售渠道购买的工业纯乙酸乙酯和石油醚, 重蒸后使用.

1.2 1,3,5-三嗪烷合成的一般步骤

在 100 mL 反应瓶中加入苄胺 (50 mmol)、多聚甲醛 (1.50 g, 50 mmol) 和 50 mL 甲苯, 100 ℃ 油浴中回流 12 h. 反应结束后降温冷却至室温, 减压蒸除溶剂, 所得混合物采用硅胶柱色谱 (石油醚：乙酸乙酯=15：1) 纯化. 得到产物 1,3,5-三嗪烷衍生物 (90% 收率).

1.3 氢胺羰基化反应的一般步骤

将烯烃 (**1**)(0.3 mmol), 1,3,5-三嗪烷衍生物 (**2**) (0.15 mmol), $Pd(P^tBu_3)_2$(7.7 mg, 0.015 mmol), HCl (150 μL, 0.6 mmol, 4.0 mol/L in 1,4-dioxane) 和苯甲腈 (4 mL) 加入干燥的安瓿瓶; 将安瓿瓶置于高压釜中, 并密封釜体; 高压釜内充入 CO(2.0 MPa) 并置换 3 次后, 将其置于 130 ℃ 的油浴中搅拌; 反应 12 h 后, 将高压釜冷却至室温, 并在通风橱中缓慢释放多余的 CO; 减压除去溶剂, 所得混合物采用硅胶柱色谱纯化, 淋洗剂为石油醚：乙酸乙酯= 10：1~5：1, 可得到酰胺产物 (**3**). 产物 (**3a**–**3r**) 表征数据如下:

N-benzyl-*N*-methyl-2-phenylpropanamide (**3a**): 53.1 mg 无色油状液体, 收率 70%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.41-6.86 (m, 10H), 4.67-4.10 (m, 2H), 3.82 (dq, *J* = 22.4, 6.8 Hz, 1H), 2.79 (d, *J* = 56.4 Hz, 3H), 1.40 (dd, *J* = 11.2, 6.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 174.20, 173.79, 141.97, 141.75, 137.49, 136.74, 128.91, 128.85, 128.51, 127.92, 127.53, 127.42, 127.32, 127.23, 126.89, 126.80, 126.29, 52.96, 51.20, 43.53, 43.16, 34.76, 34.25, 21.01, 20.85.

N-benzyl-2-(4-chlorophenyl)-*N*-methylpropanamide (**3b**): 54.2 mg 无色油状液体, 收率 63%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.31-6.94 (m, 9H), 4.69-4.16 (m, 2H), 3.81 (dq, *J* = 25.2, 7.0 Hz, 1H), 2.80 (d, *J* = 57.6 Hz, 3H), 1.38 (dd, *J* = 11.4, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 172.85, 172.34, 139.27, 139.14, 136.25, 135.48, 131.69, 131.60, 127.95, 127.90, 127.77, 127.70, 127.52, 126.88, 126.59, 126.30, 125.09, 51.99, 50.22, 41.73, 41.33, 33.74, 33.42, 19.85, 19.69.

N-benzyl-2-(3-chlorophenyl)-*N*-methylpropanamide (**3c**): 41.3 mg 无色油状液体, 收率 48%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.28-6.95 (m, 9H), 4.70-4.16 (m, 2H), 3.80 (dq, *J* = 24.4, 6.8 Hz, 1H), 2.80 (d, *J* = 63.3 Hz, 3H), 1.38 (dd, *J* = 12.4, 6.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.64, 173.16, 143.80, 143.66, 137.27, 136.48, 134.66, 130.13, 128.95, 128.64, 128.59, 127.97, 127.92, 127.65, 127.59, 127.35, 127.15, 126.16, 125.64, 53.08, 51.32, 43.13, 42.71, 34.87, 34.57, 20.91, 20.71.

N-benzyl-2-(2-chlorophenyl)-*N*-methylpropanamide (**3d**): 47.4 mg 无色油状液体, 收率 55%, 非对映异构体 (dr = 64:36). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.38-6.93 (m, 9H), 4.65-4.11 (m, 3H), 2.76 (d, *J* = 74.4 Hz, 3H), 1.36 (dd, *J* = 13.7, 6.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.81, 173.51, 139.48, 139.30, 137.37, 136.55, 132.86, 132.55, 129.55, 129.49, 128.73, 128.52, 128.46, 128.24, 128.20, 127.98, 127.62, 127.55, 127.44, 127.29, 126.44, 52.85, 51.25, 39.82, 39.29, 34.42, 34.18, 19.31, 18.76.

N-benzyl-2-(4-fluorophenyl)-*N*-methylpropanamide (**3e**): 42.3 mg 无色油状液体, 收率 52%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.37-6.81 (m, 9H), 4.76-4.10 (m, 2H), 3.82 (dq, *J* =

23.6, 6.9 Hz, 1H), 2.81 (d, *J* = 53.5 Hz, 3H), 1.38 (dd, *J* = 11.4, 6.9 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.66, 162.94, 160.49, 137.36, 136.59, 128.98, 128.91, 128.55, 127.90, 127.60, 127.31, 126.17, 115.76, 115.55, 53.02, 51.22, 42.58, 42.19, 34.77, 34.40, 21.05, 20.86. ^{19}F NMR (376 MHz, chloroform-*d*) *δ* −115.95, −116.00.

N-benzyl-2-(4-bromophenyl)-*N*-methylpropanamide (**3f**): 55.6 mg 黄色油状液体, 收率 56%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.45-7.00 (m, 9H), 4.73-4.24 (m, 2H), 3.86 (dq, *J* = 25.9, 7.0 Hz, 1H), 2.88 (d, *J* = 58.3 Hz, 3H), 1.46 (td, *J* = 12.3, 11.3, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.78, 173.26, 140.85, 140.72, 137.30, 136.53, 131.95, 129.19, 129.13, 128.94, 128.57, 127.93, 127.63, 127.35, 126.12, 120.79, 120.71, 53.03, 51.26, 42.85, 42.44, 34.78, 34.47, 20.85, 20.70.

N-benzyl-*N*-methyl-2-(*p*-tolyl)propanamide (**3g**): 54.5 mg 无色油状液体, 收率 68%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.34-7.02 (m, 9H), 4.79-4.13 (m, 2H), 3.85 (dq, *J* = 24.6, 6.8 Hz, 1H), 2.86 (d, *J* = 55.5 Hz, 3H), 2.32 (s, 3H), 1.45 (dd, *J* = 11.0, 6.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 174.37, 173.94, 138.97, 138.76, 137.56, 136.84, 136.50, 136.37, 129.58, 129.53, 128.85, 128.50, 127.95, 127.49, 127.28, 127.20, 127.18, 126.27, 52.94, 51.18, 43.11, 42.75, 34.75, 34.26, 21.05, 20.94.

N-benzyl-2-(4-(*tert*-butyl)phenyl)-*N*-methylpropanamide (**3h**): 55.6 mg 无色油状液体, 收率 60%, 非对映异构体 (dr = 52:48). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.34-6.96 (m, 9H), 4.76-4.23 (m, 2H), 3.88 (dq, *J* = 21.3, 6.9 Hz, 1H), 2.87 (d, *J* = 42.0 Hz, 3H), 1.47 (dt, *J* = 10.5, 5.7 Hz, 3H), 1.30 (d, *J* = 1.5 Hz, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 174.44, 174.13, 149.70, 149.59, 138.82, 138.52, 137.56, 136.78, 128.79, 128.48, 127.93, 127.46, 127.19, 127.06, 126.98, 126.39, 125.78, 125.67, 125.56, 52.99, 51.18, 42.90, 42.65, 34.84, 34.45, 34.16, 31.38, 20.91, 20.72.

N-benzyl-*N*-methyl-2-phenylbutanamide (**3i**): 39.2 mg 无色油状液体, 收率 49%, 非对映异构体 (dr = 57:43). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.28-6.95 (m, 10H), 4.75-4.13 (m, 2H), 3.53 (dt, *J* = 29.6, 7.4 Hz, 1H), 2.81 (d, *J* = 36.9 Hz, 3H), 2.08 (ddt, *J* = 13.6, 9.9, 7.4 Hz, 1H), 1.68 (ddt, *J* = 18.3, 13.6, 7.3 Hz, 1H), 0.80 (dt, *J* = 25.1, 7.3 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.56, 173.28, 140.37, 140.00, 137.54, 136.84, 128.84, 128.77, 128.68, 128.61, 128.50, 128.10, 128.05, 127.87, 127.84, 127.51, 127.19, 126.93, 126.88, 126.29, 71.73, 68.25, 52.89, 51.12, 50.98, 50.75, 34.79, 34.24, 28.59, 28.28.

N-benzyl-*N*-methyl-2-(naphthalen-2-yl)propanamide (**3j**): 60.0 mg 黄色油状液体, 收率 66%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.76 -6.96 (m, 12H), 4.73-4.05 (m, 2H), 3.97 (dq, *J* = 24.2, 6.8 Hz, 1H), 2.81 (d, *J* = 65.5 Hz, 3H), 1.47 (dd, *J* = 9.9, 6.8 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.70, 139.42, 139.24, 137.46, 136.74, 133.63, 132.45, 132.39, 128.90, 128.74, 128.69, 128.54, 127.95, 127.73, 127.67, 127.65, 127.54, 127.26, 126.22, 126.20, 125.83, 125.80, 125.77, 125.74, 125.65, 53.03, 51.28, 43.71, 43.33, 34.88, 34.41, 21.03, 20.88.

N-benzyl-*N*-methylcyclopentanecarboxamide (**3k**): 26.7 mg 无色油状液体, 收率 41%, 非对映异构体 (dr = 44:56). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.32-7.07 (m, 5H), 4.53 (s, 2H), 2.90-2.81 (d, 4H), 1.87-1.61 (m, 6H), 1.55-1.44 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 176.89, 176.29, 137.77, 137.04, 128.86, 128.55, 127.94, 127.50, 127.20, 126.30, 53.17, 50.94, 41.37, 41.17, 34.73, 34.02, 30.75, 30.11, 26.13, 26.10.

N-benzyl-*N*,2-dimethyldodecanamide (**3l**): 31.4 mg 无色油状液体, 收率 33%, 非对映异构体 (dr = 58:42). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.33-7.05 (m, 5H), 4.50 (d, *J* = 23.0 Hz, 2H), 2.86 (d, *J* = 9.9 Hz, 3H), 2.30 (t, *J* = 7.8 Hz, 2H), 1.61 (d, *J* = 7.3 Hz, 2H), 1.20 (q, *J* = 6.7, 6.3 Hz, 18H), 0.81 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 173.78, 173.41, 137.54, 136.75, 128.89, 128.63, 128.55, 128.01, 127.76, 127.56, 127.27, 126.28, 53.39, 50.76, 43.41, 34.84, 33.88, 33.58, 33.16, 31.93, 29.68, 29.65, 29.55, 29.52, 29.49, 29.44, 29.36, 25.47, 25.22, 22.70, 14.14.

N-(4-fluorobenzyl)-*N*-methyl-2-phenylpropanamide (**3m**): 63.4 mg 黄色油状液体, 收率 78%, 非对映异构体 (dr = 64:36). ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.26-6.85 (m, 9H), 4.68-4.14 (m, 2H), 3.81 (dq, *J* = 20.1, 6.8 Hz, 1H), 2.77 (d, *J* = 44.9 Hz, 3H), 1.46-1.37 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 174.09, 173.83, 141.85, 141.60, 133.20, 132.27, 129.61,

129.53, 128.97, 128.87, 128.64, 128.03, 127.95, 127.59, 127.36, 127.30, 127.23, 126.96, 126.86, 115.83, 115.62, 115.45, 115.23, 52.30, 50.58, 43.53, 43.26, 34.75, 34.04, 21.01, 20.79. ^{19}F NMR (376 MHz, chloroform-*d*) δ −114.94, −115.44.

N-(4-chlorobenzyl)-*N*-methyl-2-phenylpropanamide (**3n**): 49.9 mg 无色油状液体, 收率 58%, 非对映异构体 (dr = 64:36). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.26-6.81 (m, 9H), 4.66-4.16 (m, 2H), 3.90-3.72 (m, 1H), 2.77 (d, *J* = 45.3 Hz, 3H), 1.39 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 174.08, 173.86, 141.80, 141.56, 136.03, 135.18, 133.33, 133.03, 129.26, 128.99, 128.90, 128.66, 127.71, 127.37, 127.28, 126.99, 126.90, 52.37, 50.66, 43.51, 43.27, 34.85, 34.14, 21.02, 20.79.

N-(4-bromobenzyl)-*N*-methyl-2-phenylpropanamide (**3o**): 50.6 mg 黄色油状液体, 收率 51%, 非对映异构体 (dr = 64:36). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34-6.75 (m, 9H), 4.77-4.03 (m, 2H), 3.79 (dq, *J* = 35.1, 6.8 Hz, 1H), 2.77 (d, *J* = 44.8 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 174.12, 173.90, 141.76, 141.53, 136.53, 135.70, 131.94, 131.61, 129.61, 129.00, 128.90, 128.63, 128.05, 127.59, 127.36, 127.27, 127.18, 127.00, 126.92, 121.38, 121.13, 52.44, 50.73, 43.51, 43.28, 34.87, 34.17, 21.01, 20.78.

N-methyl-*N*-(4-methylbenzyl)-2-phenylpropanamide (**3p**): 63.3 mg 无色油状液体, 收率 79%, 非对映异构体 (dr = 57:43). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.25-6.81 (m, 9H), 4.64-4.01 (m, 2H), 3.81 (dq, *J* = 13.7, 6.8 Hz, 1H), 2.77 (d, *J* = 57.3 Hz, 3H), 2.24 (d, *J* = 11.3 Hz, 3H), 1.45-1.37 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 174.13, 173.69, 142.06, 141.81, 137.24, 136.86, 134.46, 133.65, 129.52, 129.17, 128.90, 128.83, 127.96, 127.42, 127.32, 126.86, 126.77, 126.28, 52.71, 50.88, 43.54, 43.14, 34.63, 34.15, 21.09, 21.07, 21.03, 20.86.

N-(4-methoxybenzyl)-*N*-methyl-2-phenylpropanamide (**3q**): 50.1 mg 无色油状液体, 收率 59%, 非对映异构体 (dr = 55:45). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33-6.69 (m, 9H), 4.56-4.09 (m, 2H), 3.83 (q, *J* = 6.8 Hz, 1H), 3.71 (d, *J* = 6.6 Hz, 3H), 2.76 (d, *J* = 52.4 Hz, 3H), 1.54-1.34 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 174.05, 173.67, 158.84, 142.06, 141.80, 129.60, 129.32, 128.91, 128.83, 128.56, 127.63, 127.39, 127.34, 126.88, 126.76, 114.21, 113.87, 55.32, 55.26, 52.38, 50.57, 43.54, 43.15, 34.55, 33.96, 21.02, 20.84.

N-(4-(*tert*-butyl)benzyl)-*N*-methyl-2-phenylpropanamide (**3r**): 54.7 mg 无色油状液体, 收率 59%, 非对映异构体 (dr = 55:45). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34-6.84 (m, 9H), 4.73-4.05 (m, 2H), 3.82 (dq, *J* = 14.0, 6.8 Hz, 1H), 2.79 (d, *J* = 53.6 Hz, 3H), 1.40 (t, *J* = 7.4 Hz, 3H), 1.23 (d, *J* = 8.9 Hz, 9H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.11, 172.64, 149.49, 149.06, 141.01, 140.80, 133.37, 132.60, 127.83, 127.79, 126.58, 126.38, 126.27, 125.79, 125.72, 124.98, 124.70, 124.34, 51.59, 49.79, 42.48, 42.04, 33.74, 33.47, 33.42, 33.19, 30.31, 20.01, 19.85.

2 结果与讨论

2.1 反应条件优化

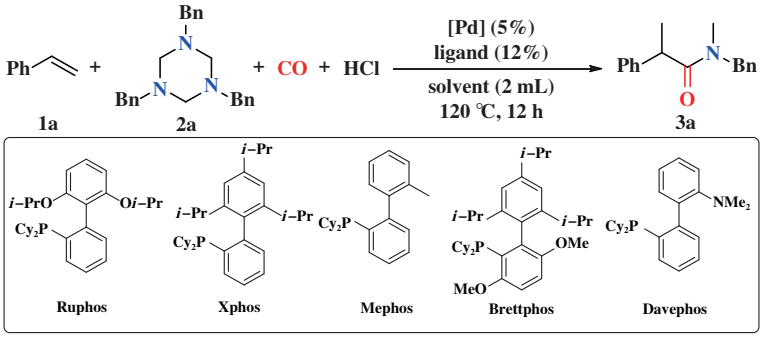
我们使用苯乙烯 (**1a**) 和 1,3,5-三苄基-1,3,5-三嗪烷 (**2a**) 为模板底物, 尝试考察钯催化氢胺羰基化反应的最佳反应条件 (表 1). 当使用 $PdCl_2$ 为催化剂前体、Ruphos 为配体、苯甲醚为溶剂, 以及 2 mol/L 的 HCl(4.0 mol/L 的 1,4-二氧六环溶液) 时, 在 2.0 MPa 的 CO 气氛中, 120 ℃ 下反应 12 h 后, 可生成烷基支链酰胺化合物 (**3a**), 收率为 51%(Entry1). 考察钯前体 (Entry 1−8) 和膦配体 (Entry 9−14) 对反应效果的影响时, 发现配有大位阻膦配体的零价钯—$Pd(P^tBu_3)_2$ 更有利于目标产物的生成 (表 1, Entry 8, 53% 的产率). 随后, 我们研究了大、小极性, 以及质子、非质子类型的溶剂对反应的影响 (Entry 15−20), 并确定了最佳溶剂为苯甲腈, 其用量为 4 mL (Entry 21−22). 当使用 HBr、甲酸、氯化铵或盐酸羟胺代替 HCl 时, 反应无法进行 (Entry 23−28). 在对 CO 压力和反应温度进行研究后 (Entry 29−30), 我们确定最佳的氢胺羰基化反应条件为: $Pd(P^tBu_3)_2$ 作催化剂、4 mL 的苯甲腈作溶剂、CO 压力为 2.0 MPa、温度为 130 ℃、反应时间为 12 h, 且可生成的酰胺化合物 (**3a**) 的气相收率为 72%、分离收率为 70%.

2.2 底物适应性考察

确定最佳反应条件后, 我们首先对烯烃 (**1**) 的底物适应性进行了考察 (表 2). 在研究芳基烯烃中芳环上的吸电子取代基对反应的影响时, 发现邻、

表 1 反应条件优化[a]

Table 1 Optimization of the reaction conditions[a]



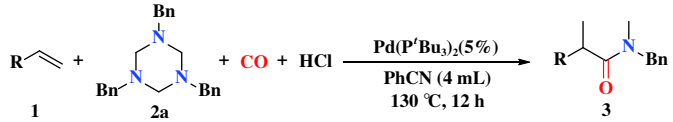
Entry	Palladium catalyst	Ligand	Solvent	Yield/%[b]
1	$PdCl_2$	Ruphos	anisole	51
2	$PdBr_2$	Ruphos	anisole	0
3	PdI_2	Ruphos	anisole	0
4	$Pd(MeCN)_2Cl_2$	Ruphos	anisole	18
5	$Pd(OAc)_2$	Ruphos	anisole	27
6	$Pd(PhCN)_2Cl_2$	Ruphos	anisole	20
7	$[Pd(allyl)Cl]_2$	Ruphos	anisole	Trace
8	$Pd(P^tBu_3)_2$	–	anisole	53
9	$PdCl_2$	PPh_3	anisole	0
10	$PdCl_2$	PCy_3	anisole	0
11	$PdCl_2$	Xphos	anisole	Trace
12	$PdCl_2$	Mephos	anisole	0
13	$PdCl_2$	Brettphos	anisole	29
14	$PdCl_2$	Davephos	anisole	13
15	$Pd(P^tBu_3)_2$	–	THF	45
16	$Pd(P^tBu_3)_2$	–	toluene	20
17	$Pd(P^tBu_3)_2$	–	1,4-dixoane	35
18	$Pd(P^tBu_3)_2$	–	^{n}BuOH	0
19	$Pd(P^tBu_3)_2$	–	NMP	0
20	$Pd(P^tBu_3)_2$	–	DMSO	0
21	$Pd(P^tBu_3)_2$	–	PhCN	60
22[d]	$Pd(P^tBu_3)_2$	–	PhCN	69
23[d,e]	$Pd(P^tBu_3)_2$	–	PhCN	0
24[d,f]	$Pd(P^tBu_3)_2$	–	PhCN	0
25[d,g]	$Pd(P^tBu_3)_2$	–	PhCN	0
26[d,h]	$Pd(P^tBu_3)_2$	–	PhCN	0
27[d,i]	$Pd(P^tBu_3)_2$	–	PhCN	30
28[d,j]	$Pd(P^tBu_3)_2$	–	PhCN	57
29[d,k]	$Pd(P^tBu_3)_2$	–	PhCN	30
30[d,l]	$Pd(P^tBu_3)_2$	–	PhCN	72(70[c])

a: Reaction conditions: **1a** (0.3 mmol), **2a** (0.15 mmol), HCl (0.6 mmol, 4.0 mol/L in 1,4-dioxane), palladium catalyst (0.015 mmol), ligand(0.036 mmol), CO(2.0 MPa), solvent (2 mL), 120 ℃, 12 hours; b: Yields were determined by GC-analysis using *n*-hexadecane as an internal standard; c: Isolated yield; d: PhCN (4 mL); e: HBr instead of HCl; f: HCO_2 Hinstead of HCl; g: NH_4 Clinstead of HCl; h: $NH_2OH{\cdot}H_2O$ Clinstead of HCl; i: HCl(0.3 mmol); j: HCl (0.9 mmol); k: CO (1.0 MPa); l: 130 ℃

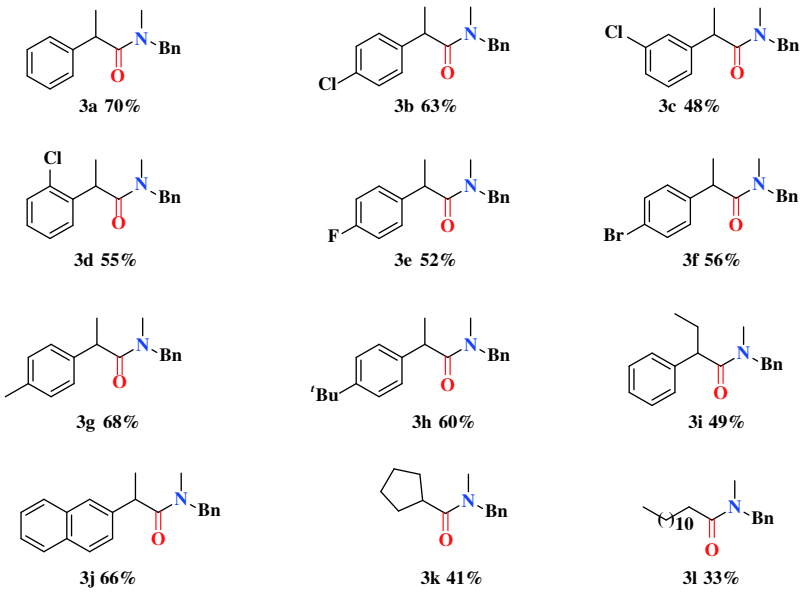
间、对-氯取代的芳基烯烃, 以及氟或溴取代的芳香烯烃都可较好地兼容该反应, 并以中等收率转化成烷基支链酰胺化合物 (**3b**−**3f**). 当烯烃的芳环上含供电子取代基团时 (甲基或叔丁基), 可得到中等以上产率的酰胺产物 (**3g** 和 **3h**). 除端烯化合物外, 内烯 (*β*-甲基苯乙烯) 也可发生氢胺羰基化反应, 并转化

表 2 烯烃底物适应性考察[a]

Table 2 Substrate scope for alkenes[a]



1 2a 3



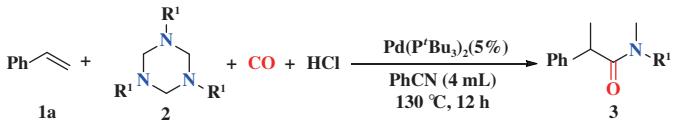
a: Reaction conditions: 1 (0.3 mmol), 2a (0.15 mmol), HCl (0.6 mmol, 4.0 mol/L in 1,4-dioxane), Pd(PtBu$_3$)$_2$ (0.015 mol), CO(2.0 MPa), PhCN (4 mL), 130 ℃, 12 hours, isolated yields

为目标化合物 (**3i**). 此外, 稠环烯烃—乙烯基萘也可转化为 66% 的酰胺产物 (**3j**). 除芳香烯烃底物外, 我们也对脂肪族烯烃的底物适应性进行了考察. 尽管得到的酰胺化合物 **3k** 和 **3l** 产率略低, 但环状和直链脂肪烯烃 (环戊烯和正十二烯) 均可顺利转化为相应产物, 且当正十二烯作底物时, 仅选择性地得到直链产物 **3l**, 而无异构化的支链产物生成.

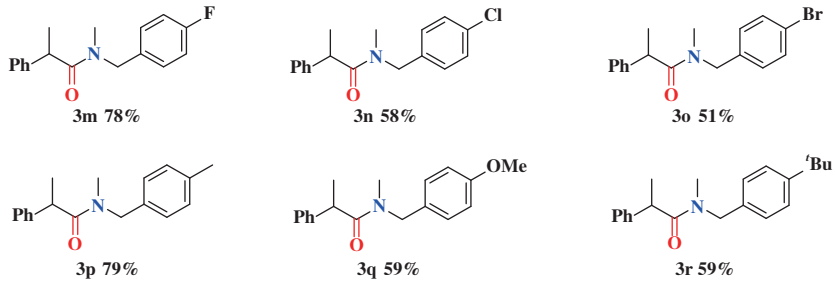
随后, 我们进一步对 1,3,5-三嗪烷的底物适应性进行了考察 (表 3). 当 1,3,5-三嗪烷的芳环上含有吸电子取代基时 (如: 氟、氯、溴), 可以中等至良好

表 3 1,3,5-三嗪烷底物适应性考察[a]

Table 3 Substrate scope for 1,3,5-triazines[a]



1a 2 3



a: Reaction conditions: 1a (0.3 mmol), 2 (0.15 mmol), HCl (0.6 mmol, 4.0 mol/L in 1,4-dioxane), Pd(PtBu$_3$)$_2$ (0.015 mol), CO(2.0 MPa), PhCN (4 mL), 130 ℃, 12 hours, isolated yields

的收率得到相应的烷基支链酰胺产物 (**3m**−**3o**). 当芳环上的取代基为供电子基团时 (如: 甲基、甲氧基以及大位阻的叔丁基), 也可转化为相应的目标化合物 (**3p**−**3r**).

2.3 反应机理推测

基于上述研究工作和已报道的相关研究, 我们提出了钯催化的烯烃氢胺碳基化过程可能的反应机理 (图 3): Pd(0) 与 HCl 发生氧化加成反应, 生成钯-

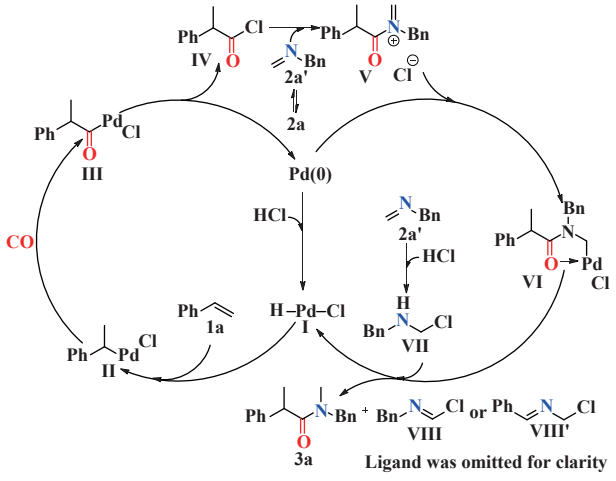


图 3　可能的反应机理

Fig.3 Possiblereaction mechanism

负氢中间体 (Ⅰ); 苯乙烯对钯-负氢物种 (Ⅰ) 进行迁移插入反应后生成烷基-钯中间体 (Ⅱ); CO 插入烷基-钯 (Ⅱ) 后得到酰基-钯中间体 (Ⅲ)[32−34]; 酰基-钯 (Ⅲ) 发生还原消除反应, 生成 Pd(0) 和酰氯 (Ⅳ); 而 (Ⅳ) 可与 1,3,5-三苄基-1,3,5-三嗪烷 (**2a**) 分解产生的亚胺 (**2a'**)[35−37] 反应, 生成亚胺盐 (Ⅴ)[38]; 亚胺盐 (Ⅴ) 与 Pd(0) 发生氧化加成反应, 得到烷基-钯中间体 (Ⅵ); 由于亚胺 (**2a'**) 可与 HCl 反应生成二级胺 (Ⅶ)[35], 而 (Ⅶ) 恰好可为烷基-钯中间体 (Ⅵ) 提供氢源, 从而最终生成酰胺 (**3a**)、亚胺 (Ⅷ或Ⅷ') 和钯-负氢物种 (Ⅰ); 钯-负氢物种 (Ⅰ) 发生还原消除反应后生成 Pd(0), 从而完成催化循环.

3 结论

综上所述, 首次使用容易制备的脂肪族三级胺—环状 1,3,5-三嗪烷化合物作胺源, 实现了钯催化的烯烃氢胺羰基化反应. 1,3,5-三嗪烷作为脂肪胺的替代物, 解决了本领域研究中脂肪胺对钯-负氢物种的毒化问题, 合成了多种 *N*-烷基支链酰胺类化合物. 该反应条件温和, 且具有较好的官能团兼容性, 为钯催化的烯烃氢胺羰基化反应提供了新的思路.

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Palladium-catalyzed Hydroaminocarbonylation of Alkene with Triazine

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Abstract: Amide compounds are widely used in medicine, pesticides, materials, synthetic chemistry and other fields. Therefore, the new and efficient synthesis methods of amides haveattracted high attention of chemists. In this approach, cyclic aliphatic tertiary amine 1,3,5-triazine was first applied as the amine source in the hydroaminocarbonylation transformation of alkene via palladium catalysis, affording virous alkyl branched amide compounds. Additionally, the problem of palladium catalyst poisoning by the aliphatic amine was successfully addressed by this protocol. Furthermore, a possible reaction mechanism is proposed.

Key words: palladium catalysis; alkene; 1,3,5-triazine; hydroaminocarbonylation; alkyl branched amide