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腙为配体的高效铜催化的胺的 *N*-芳基化反应

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摘要： 发展了一种温和、高效的以腙为配体的铜催化系统，在相对温和的条件下，将该系统用于催化胺与芳卤的 *N*-芳基化反应，得到了良好的分离收率. 腙配体是稳定的、价廉的，并易于通过简单的方法，从市场可得的原料制备.

关键词： 胺；芳卤；腙；*N*-芳基化
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由于含有 *N*-芳基组成部分的化合物在天然产物领域[1]、光学领域[2]及材料学领域[3]的重要性，这类化合物的合成近年来引起了人们的极大兴趣. 钯催化的 Ullmann 类型的偶联反应是组装这类化合物的传统方法，近些年来得到了快速的发展[4-6]. 然而从经济角度看，在温和条件下以铜为媒介的反应已经成为工业规模化生产研究的焦点[7-8]. 最近，发展了许多在温和条件下用于催化胺化反应的配体，例如 1, 10-菲咯啉[9-11]、反式-1, 2-环己二胺[12-13]、乙二醇[14]、氨基酸[15-16]、NHC 型配体[17]、1, 3-二酮[18-21]、N-氧型[22-23]及其他类型含有氮和氧的配体[24-31]. 可是，妨碍其应用的两个重要因素是催化剂的费用和可利用性，特别是某些配体的制备要经过繁琐的多步合成过程. 因此，发现更加经济、高效的配体仍然迫在眉睫. 基于此，我们一直致力于瞄准发展低成本且易于合成的配体，这些配体大都是从廉价的起始原料，经过简单的步骤制备. 最近的突破是发展了分别用于脂肪胺及含氮杂环的 *N*-芳基化反应的配体[32-33]. 我们应用腙和肟配体于铜催化的胺的 *N*-芳基化反应中，结果发现不仅用 Cu_2O 作催化剂前体时腙是高效的配体，而且配体是低费用的、容易制备的及空气中稳定的.

1 实验部分

1.1 材料和方法

熔点的测定由 YAZAWA 微量熔点仪(未校正)完成. 以 TMS 作内标，$CDCl_3$ 作溶剂，使用 Varian 核磁共振仪(400 MHz, USA)测定 ^{1}H NMR 和 ^{13}C NMR 谱. 以乙腈作溶剂，通过 Mariner 5303 高分辨质谱仪(USA)测定配体及产物的高分辨质谱(HRMS).

所有偶联反应在氩气氛围下进行. 使用硅胶柱提纯偶联产物. 所有溶剂均按照标准方法进行干燥和脱气. 使用沸点范围为 60 ~ 90 ℃的石油醚. 通过改变石油醚与乙酸乙酯的比例来调节洗脱液的极性梯度，直至将产物分开.

1.2 配体的合成

将(取代)肼或羟胺 H_2N-R^2(10 mmol，图示 1)和甲苯(6 mL，对于 a)或三乙胺(6 mL，对于 b，c)加入到装有磁搅拌子的 50 mL 干燥的圆底烧瓶中. 在搅拌下，滴加 R^1-CHO(10 mmol)的 6 mL 甲苯溶液. 然后，在搅拌下加热反应混合物至 85 ℃并反应 24 h. 冷却到室温后，加入 4 mL 乙醇到混合物中. 滤除固体，减压下除去溶剂. 用乙醇对粗产物进行重结晶得到目标化合物.

1.3 偶联反应

将 Cu_2O (14.4 mg, 0.1 mmol)、Cs_2CO_3(977.5 mg, 3 mmol) 及配体 **4a** (43.2 mg, 0.2 mmol)加入到 Schlenk 瓶中. 对 Schlenk 瓶抽空并置换成氩气(5 次)氛围. 在室温下加入 DMSO (1 mL)、胺(1.5 mmol)和芳碘(杂芳溴)(1 mmol). 再次抽空置换 Schlenk 瓶成氩气氛围(5 次). 在 95 ℃搅拌下加热

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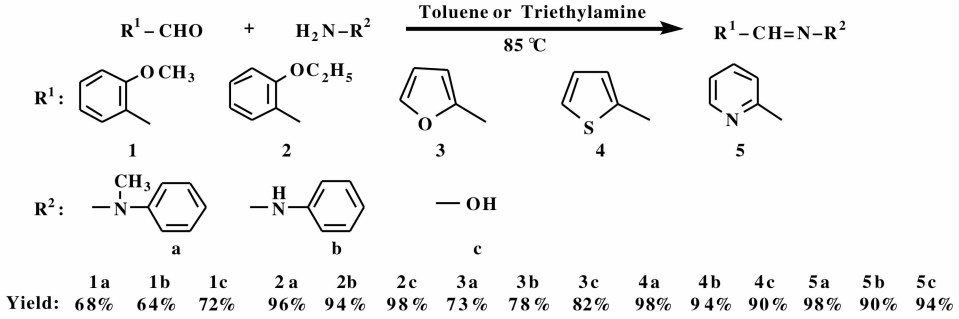
反应混合物 36 h. 冷却到室温后，将 4 mL 乙酸乙酯和 10 mL 水加入到反应瓶中. 分出有机层，水层进一步用乙酸乙酯萃取(4×10 mL). 合并有机相，用饱和食盐水洗涤后，无水 Na_2SO_4 干燥. 真空下除去溶剂，剩余物进一步通过硅胶柱纯化得到目标产物.

2 结果与讨论

如图示 1 所示，腙和肟配体 **1a**、**1b**、**1c**、**2a**、**2b**、**2c**、**3a**、**3b**、**3c**、**4a**、**4b**、**4c**、**5a**、**5b** 及 **5c** 可以通过简单的一步反应，由廉价、易得的(取代)肼或羟胺及相应的醛以优良的分离收率合成.



图示 1 腙及肟配体的合成

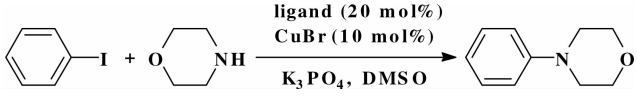
Scheme 1 Synthesis of hydrazone and oxime ligand

仅利用萃取和重结晶而不是使用复杂的分离过程得到配体，而且数周内它们在空气中稳定存在.

在初步的筛选实验中，K_3PO_4 作为碱，在 95 ℃ 及 CuBr 存在下，使用碘苯与吗啉在 DMSO 中的偶联反应作为模板反应. 将合成的腙和肟分别用于碘苯和吗啉的偶联反应中，其反应结果总结于表 1 中.

表 1 铜催化吗啉的 *N*-芳基化反应：配体的筛选[a]

Table 1 Copper-catalyzed *N*-arylation of morpholine: screening of ligands[a]



Entry	Ligand	Base	Solvent	Yield/%[b]
1	**1a**	K_3PO_4	DMSO	33
2	**1b**	K_3PO_4	DMSO	36
3	**1c**	K_3PO_4	DMSO	29
4	**2a**	K_3PO_4	DMSO	31
5	**2b**	K_3PO_4	DMSO	33
6	**2c**	K_3PO_4	DMSO	28
7	**3a**	K_3PO_4	DMSO	25
8	**3b**	K_3PO_4	DMSO	38
9	**3c**	K_3PO_4	DMSO	35
10	**4b**	K_3PO_4	DMSO	38
11	**5b**	K_3PO_4	DMSO	28
12	**4a**	K_3PO_4	DMSO	40
13	**4c**	K_3PO_4	DMSO	24
14	**5a**	K_3PO_4	DMSO	21
15	**5c**	K_3PO_4	DMSO	38

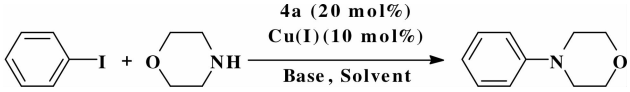
a. Reaction conditions: CuBr (0.1 mmol), ligand (0.2 mmol), PhI (1.0 mmol), morpholine (1.5 mmol), and K_3PO_4(3 mmol), DMSO (1 mL), 95 ℃, 36 h; b. Isolated yield

2-甲氧基苯甲醛缩胺比 2-乙氧基苯甲醛缩胺的效果稍好一些(表 1, Entry 1-6). 2-呋喃甲醛苯腙和 2-噻吩甲醛苯腙配体上的氧和硫对配体活性的影响几乎没有差别(表 1, Entry 8-9). 而使用 2-吡啶苯腙配体, 偶联反应的产率较低. 对于 2-噻吩甲醛苯腙配体, 观察到了较高的分离收率(表 1, Entry 10 和 12). 使用 **4a** 配体得到 40% 最好产率, 这可能与配体氮原子所连的甲基有关. 因此, 为了进一步筛选配体, 又测定了 **4c**, **5a** 和 **5c** 的活性(表 1, Entry 13-15). 不幸的是使用 **5a** 与 **4c** 作为配体, 得到了更低的结果.

为了达到有效的偶联反应, 通常选择合适的碱、溶剂及铜源是非常重要的. 因此, 使用上述筛选出的配体, 对碱、溶剂及铜源进行了优化, 所得结果列于表 2 中.

表 2 用于吗啉 *N*-芳基化反应的碱、溶剂及铜源的筛选[a]

Table 2 Optimization of base, solvent and copper source for *N*-arylation of morpholine[a]



Entry	Cu(I)	Base	Solvent	Yield/%[b]
1	CuBr	K_3PO_4	DMSO	40
2	CuBr	K_2CO_3	DMSO	16
3	CuBr	KOH	DMSO	36
4	CuBr	$KOBu^t$	DMSO	63
5	CuBr	$NaOBu^t$	DMSO	18
6	CuBr	Cs_2CO_3	DMSO	72
7	CuBr	NEt_3	DMSO	8
8	CuBr	Cs_2CO_3	DMF	33
9	CuBr	Cs_2CO_3	Dioxane	20
10	CuBr	Cs_2CO_3	Toluene	19
11	CuBr	Cs_2CO_3	CH_3CN	21
12	CuBr	Cs_2CO_3	THF	25
13	CuCl	Cs_2CO_3	DMSO	34
14	CuI	Cs_2CO_3	DMSO	58
15	Cu_2O	Cs_2CO_3	DMSO	75
16	CuCN	Cs_2CO_3	DMSO	24
17[c]	Cu_2O	Cs_2CO_3	DMSO	4
18[d]	-	Cs_2CO_3	DMSO	3

a. Reaction conditions: Cu(I) (0.1 mmol), **4a** (0.2 mmol), PhI (1.0 mmol), morpholine (1.5 mmol), base (3 mmol), solvent (1 mL), 95 ℃, 36 h; b. Isolated yield; c. No ligand was used; d. No copper salt was used.

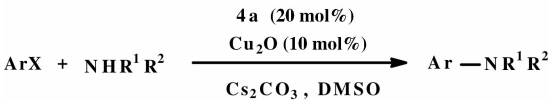
常用的碱, 如 K_3PO_4、K_2CO_3、KOH、$KOBu^t$、$NaOBu^t$、Cs_2CO_3 及 NEt_3 对偶联反应有不同的影响(表 2, Entry 1-7), 其中 Cs_2CO_3 最好(表 2, Entry 6). 其次, $KOBu^t$ 也可供选择(表 2, Entry 4). 当使用有机碱 NEt_3 时, 仅仅得到了 8% 的分离收率(表 2, Entry 7). 使用 Cs_2CO_3 作为碱, 测定溶剂影响的研究表明: 模板反应在溶剂 DMSO 中能高效进行(表 2, Entry 6), 而在 DMF、二氧六环、甲苯、CH_3CN 及 THF 中, 反应效率较低(表 2, Entry 8-12). 显然, 选择 DMSO 作为接下来实验的溶剂. 在

铜源检测中，发现空气中稳定的、廉价的 Cu_2O 更有效(表 2，Entry 15)．而没有配体只有铜源或只有铜源没有配体的情况下，仅仅观察到了很低的产率(表 2，Entry 17-18)．

扩展催化系统 Cu_2O/**4a**/Cs_2CO_3/DMSO 至其他的胺类与芳碘类化合物(表 3，Entry 1-16)、5-溴嘧啶(表 3，Entry 17-20)及 2-溴吡啶(表 3，Entry 21-24)的偶联反应，结果总结在表 3 中．

表 3 铜催化的芳卤与胺的偶联反应[a]

Table 3 Copper-catalyzed coupling reaction of aryl halides with amines[a]



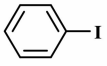
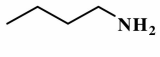
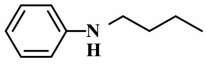
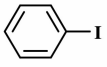
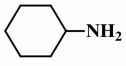
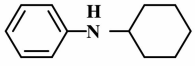
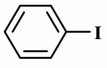
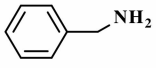
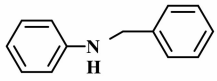
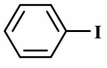
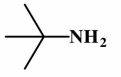
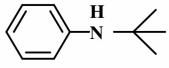
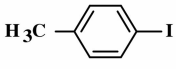
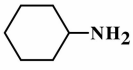
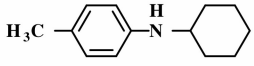
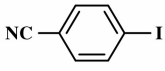
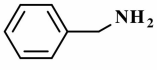
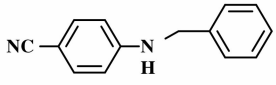
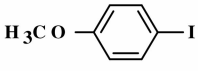
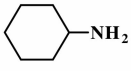
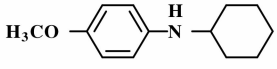
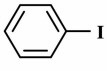
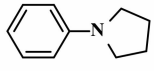
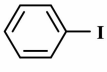
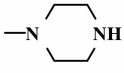
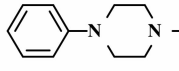
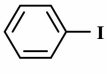
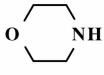
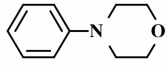
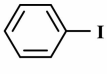
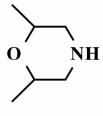
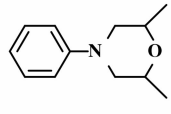
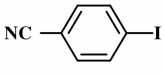
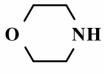
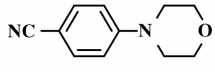
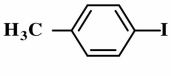
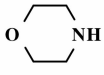
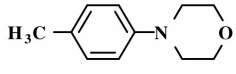
Enery	ArX	R^1R^2NH	Product	Yield /%[b]
1				71
2				72
3				72
4				68
5				67
6				75
7				64
8				74
9				70
10				75
11				72
12				80
13				69
14				66
15				65

表3(续)

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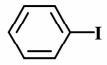
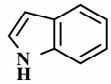
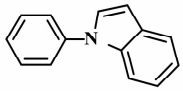
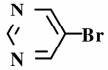
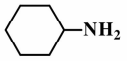
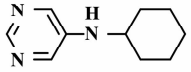
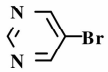
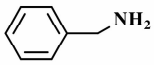
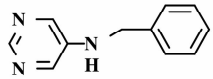
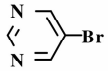
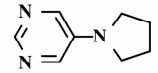
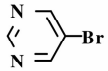
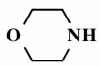
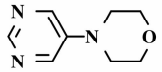
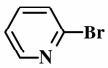
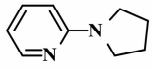
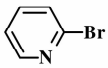
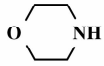
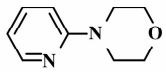
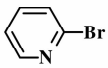
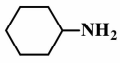
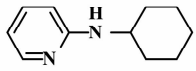
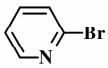
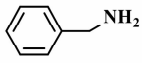
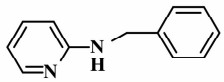
16				64
17[c]				68
18[c]				69
19[c]				67
20[c]				71
21[c]				63
22[c]				66
23[c]				65
24[c]				69

a. Reaction conditions: Cu_2O (0.1 mmol), **4a** (0.2 mmol), aryl halide (1.0 mmol), amine (1.5 mmol), and Cs_2CO_3(3 mmol) in DMSO (1 mL), 95 ℃, 36 h; b. Isolated yields; c. Reaction conditions: Cu_2O (0.2 mmol), **4a** (0.4 mmol), aryl halide (1.0 mmol), amine (1.5 mmol), and Cs_2CO_3(3 mmol) in DMSO (1 mL), 95 ℃, 48 h.

将筛选出的 Cu_2O/**4a**/DMSO/Cs_2CO_3 作为脂肪伯胺、仲胺与芳碘偶联反应的最佳催化系统. 首先, 采用伯胺作为试剂, 观察到了优良的分离收率(表3, Entry 1-7). 反应能够忍耐像氰基、甲氧基等官能团(表3, Entry 5-7). 对于取代芳碘, 观察到了电子效应的明显影响. 对含有吸电子基的芳碘, 得到了相对较高的收率(表3, Entry 2 与5, Entry 3 与6). 对含有供电子基的芳碘, 得到了相对较低的分离收率(表3, Entry 7 与2). 其次, 选用仲胺作试剂, 得到了可观的分离收率(表3, Entry 8-15). 同样, 反应也能够容忍像氰基及甲氧基等活性基团(表3, Entry 12-15). 吸电子及供电子基(表3, Entry 14 与10, Entry 15 与8)对芳碘偶联反应产率的影响与伯胺的芳基化相似.

接下来, 将 Cu_2O/**4a**/DMSO/Cs_2CO_3 作为催化系统用于脂肪胺与 *N*-杂环芳烃的偶联反应. 如表3所示, 当 Cu_2O 和配体的量加倍后, 几种 *N*-杂环化合物能有效地转化为目标产物. 5-溴嘧啶、2-溴吡啶与几种胺的偶联反应能够平稳进行(表3, Entry 17-24). 得到了良好的分离收率, 但所得结果稍有差别.

部分代表性配体及偶联反应产物的表征结果如下:

2-乙氧基苯甲醛-*N*-甲基苯胨(**4a**): 淡黄色固体, m.p. 66 ~ 67 ℃. ^{1}H NMR ($CDCl_3$): δ 8.06-8.04(d, J = 7.6 Hz, 1H), 7.94(s, 1H), 7.43-7.22(m, 5H), 7.09-6.72(m, 3H), 4.15-4.10(m, 2H), 3.45-3.30(d, J = 22.8 Hz, 3H), 1.50-1.48(t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 15.44, 33.70, 64.46, 112.60, 115.70, 120.84, 121.31, 125.91, 125.95, 128.88, 129.21, 129.47, 148.56, 156.84. HRMS (APCI) $C_{16}H_{19}N_2O$ (M + H^+): 计算 255.1447, 发现 255.1521.

2-呋喃甲醛-*N*-甲基苯胨(**5a**): 黄色固体, m.

p. 54 ~ 55 ℃. ^{1}H NMR($CDCl_3$)：δ 7.47-7.34(m, 6H), 6.96(s, 1H), 6.56(s, 1H), 6.47(s, 1H), 3.38(s, 3H). ^{13}C NMR($CDCl_3$)：δ 33.46, 107.71, 111.74, 115.78, 121.11, 123.01, 129.27, 142.42, 147.84, 152.59. HRMS(APCI) $C_{12}H_{13}N_2O$ (M+H^+)：计算 201.0956，发现 201.1029.

N-环己基苯胺(Table 3, Entry 2)：无色液体. ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.23 ~ 7.22 (d, J = 4.0 Hz, 2H), 6.74 ~ 6.66 (d, J = 32.0 Hz, 3H), 3.59 (s, 1H), 3.32 ~ 3.31 (d, J = 3.3 Hz, 1H), 2.13 (s, 2H), 1.83 ~ 1.72 (d, J = 41.8 Hz 3H), 1.52 ~ 1.01 (m, 5H). HRMS (APCI) $C_{12}H_{18}N$(M+H^+)：计算 176.1368，发现 176.1440.

N-苯基吗啉(Table 3, Entry 10)：白色固体. m. p. 50 ~ 52 ℃. ^{1}H NMR (400 MHz, $CDCl_3$)：δ 7.33 ~ 7.31 (d, J = 6.7 Hz, 2H), 6.96 ~ 6.94 (d, J = 7.5 Hz, 3H), 3.89 (s, 4H), 3.19 (s, 4H). HRMS (APCI) $C_{10}H_{14}NO$ (M+H^+)：计算 164.1001，发现 164.1073.

3 结论

总之，使用腙作为配体，发展了一种温和的、高效的胺与芳卤的 *N*-芳基化反应的铜催化系统. 配体通过简单、有效的方法，使用廉价可得的起始原料合成，并具有价廉、稳定的特点. 尽管这一方法仅限于高活性芳卤的偶联反应，这些有利的特性使得它们在某些情况下具有一定的、潜在的应用价值，并且也代表了发展简单、价廉催化系统的实际趋势. 进一步的研究正在进行中.

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Highly Efficient Copper-Catalyzed *N*-Arylation of Amine with Arylhalide Using Hydrazone as Ligand

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Abstract: The synthesis of compounds containing the *N*-aryl moiety has attracted a great deal of interest recently due to the importance of such compounds in fields as diverse as natural products, photograph, and materials. However, two major factors that hamper application are the cost and the availability of the catalysts, in particular of the ligands that are often prepared in a tedious multi-step synthesis. Therefore, the discovery of more cost-effective and highly efficient ligands is still critically desirable. For this reason, we has embarked on a program aimed at the development of ligands that are low-cost and easily prepared in few steps from readily available starting materials. First, the hydrazone and oxime ligands were prepared from inexpensive, commercially available starting materials (i. e. azanol and hydrazine) by using a simple method. Secondly, the coupling reaction of phenyl iodide with morpholine was used as model reaction using K_3PO_4 as base in the presence of CuBr under mild reaction temperature of 95 ℃ in DMSO. A variety of synthesized hydrazone and oxime ligands were respectively used for the coupling of morpholine with phenyl iodide. The best result was obtained when 2-thiofuranformaldehyde-*N*-methylphenylhydrazine (4a) was utilized as ligand. Thirdly with optimal ligand 2-thiofuranformaldehyde-*N*-methylphenylhydrazine (4a) and above model, frequently used bases (such as K_3PO_4, K_2CO_3, KOH, $KOBu^t$, $NaOBu^t$, Cs_2CO_3 and NEt_3), solvents (e. g. DMSO, DMF, dioxane, toluene, CH_3CN, THF) and copper sources (for example CuBr, CuCl, CuI, Cu_2O, CuCN) were respectively screened. It was proved that Cs_2CO_3 was the best among optimized bases and a survey determining the influence of the solvent with Cs_2CO_3 as base showed that the model reaction could be efficiently conducted in DMSO. The air-stable, inexpensive Cu_2O was the most efficient among the examined copper sources. Finally, the optimized optimal catalytic system Cu_2O/2-thiofuranformaldehyde-*N*-methylphenylhydrazine (4a)/Cs_2CO_3/DMSO was further extended to the *N*-arylation of other amines with aryl iodides, 5-bromopyrimidine and 2-bromopyridine under relative mild condition and good yields were obtained. Although this protocol is restricted to the coupling of highly activated aryl halides, these favorable characteristics make them potentially practical utility in many cases and represent an advance toward the discovery of simple, low-cost catalyst systems for eventual availability.

Key words: amine; aryl halide; hydrazone; *N*-arylation