

专 论

固相有机合成中钯催化的交叉偶联反应研究进展

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摘要: 过渡金属钯催化交叉偶联反应是形成碳-碳键的一种十分有效的方法, 因此钯催化的 C—C 偶联反应引起了更多人们的广泛关注, 并发展了多种不同的 C—C 偶联反应, 包括 Heck 反应、Negishi 反应、Suzuki 偶联和 Stille 偶联等。固相有机合成具有反应条件温和、可使多种活性官能团兼容、受空间位阻影响小、具有高度的化学选择性、毒性小、副产物少且易于分离纯化、产率高等优点, 近几年来一直是催化化学和固相合成与组合化学的研究热点。本文根据不同的分类标准结合本课题组的研究工作综述了近年来人们对 Heck 反应、Negishi 反应、Suzuki 偶联和 Stille 偶联在固相有机合成中钯催化交叉偶联反应的研究进展, 最后展望了固相合成中钯催化交叉偶联反应的研究前景。

关键词: 钯催化; 偶联反应; Heck 反应; Negishi 反应; Suzuki 偶联; Stille 偶联; 固相合成与组合化学

引言

2010 年的诺贝尔化学奖分别授予了美国 Delaware 大学名誉教授 Richard F Heck、美国 Purdue 大学教授 Ei-ichi Negishi(根岸英一)和日本 Hokkaido 大学名誉教授 Akira Suzuki(铃木章)。这三位教授分别发明了 Heck 反应(1972 年)、Negishi 反应(1977 年)和 Suzuki 反应(1979 年)而获此殊荣。上述 3 个反应已经在药物合成、先进材料制备以及电子产品制作等方面发挥重要作用。这 3 个反应同属于钯催化的交叉偶联反应, 在固相有机合成(Solid Phase Organic Synthesis, SPOS)研究领域也有广泛应用。

SPOS 始于 1963 年, 美国洛克菲勒大学 R. B. Merrifield 教授使用聚苯乙烯微球作为载体进行多肽合成并在合成结束后把多肽从树脂上切割下来^[1], 他的这一开创性成就彻底改变了合成多肽、寡聚糖等化合物的命运并于 1984 年获得诺贝尔化学奖。如今 SPOS 已经变成组合合成药物小分子库的基石^[2]。SPOS 反应的最大优点是负载在聚合物微球上的产物可以和溶液中其它过量的试剂、催化剂以及副产物通过简单过滤被分离, 从而避免了繁琐的分离步骤, 这一点对于钯催化交叉偶联反应尤为重要, 溶液中的钯催化剂可以经过滤与产物分离, 并可以通过加入过量的反应试剂而提高反应收率。目前 SPOS 使用较多的已商品化的聚合物载体见图 1。图中的小圆球代表交联聚苯乙烯微球。

1 在聚合物载体上进行的 Heck 反应

典型的 Heck 反应是在 $\text{Pd}(\text{OAc})_2$ 或 $\text{Pd}_2(\text{dba})_3$ 的催化下发生在碘代芳烃与烯烃之间的偶联反应, 并形成了新的 C—C 键。由于反应条件温和且不影响化合物中的其它官能团, Heck 反应已经成功广泛使用于固相有机合成。

1.1 分子间的 Heck 反应

Heck 反应能够广泛应用于 SPOS 是由于起始原料烯烃或者卤代芳烃易得^[4]。SPOS 条件下的 Heck

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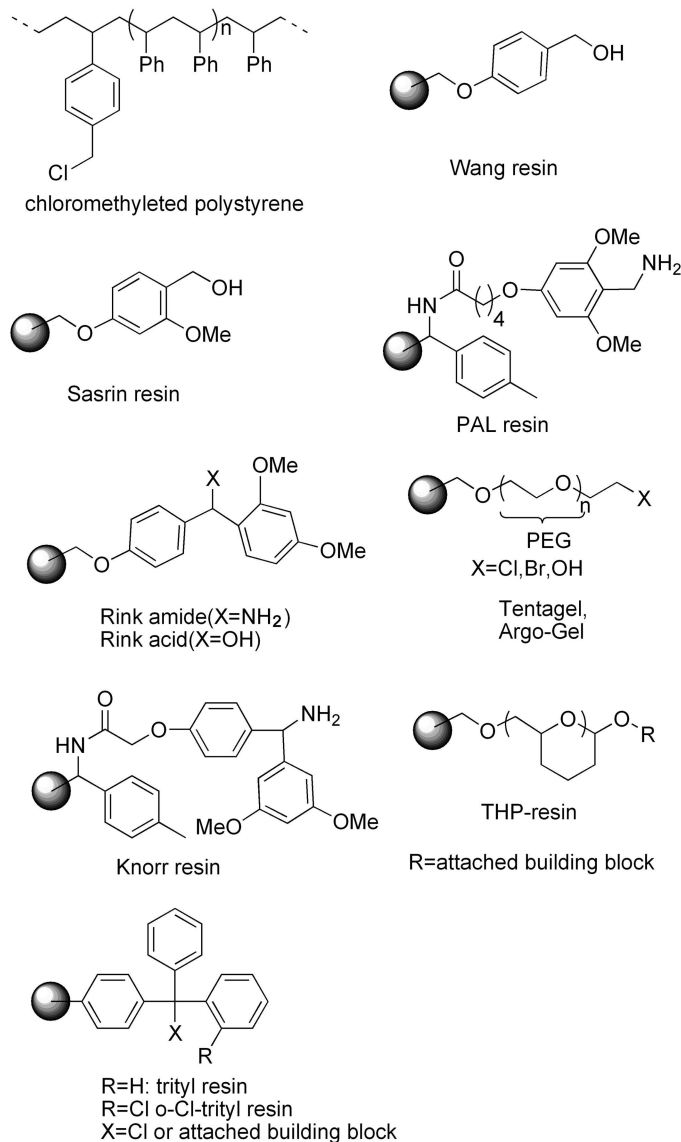


图 1 固相载体上用于钯催化和中间态反应的多种功能性的聚苯乙烯树脂^[3]

Figure 1 Types of functionalised polystyrene resins used for palladium-catalysed and -mediated reactions on solid supports (for reviews and explanations see Ref.[3])

反应可分为标准 Heck 反应条件[Pd(OAc)₂, PPh₃ 或 P(o-Tol)₃, DMF, 80 ~ 100 °C, 2 ~ 24h]^[4] 或者 Jeffery 发展的 Heck 反应条件[Pd(OAc)₂, PPh₃, Bu₄NCl, K₂CO₃, DMF, 20 ~ 80 °C]^[5]。在 Jeffery 反应条件下为了提高收率常常加入 10% 的水。在有些条件下, 使用 Pd₂(dba)₃ 比 Pd(OAc)₂ 更有效^[6]。

SPOS 条件下的 Heck 反应是将卤代芳烃连接在聚合物载体上(大多数情况下是碘代芳烃或者碘盐)和可溶性的烯反应(见表 1)或者是将烯烃固定在载体和可溶性的卤代芳烃反应(见表 2)。对于同类型的聚合物载体和同类型的催化体系, 固载碘代芳烃比固载烯烃更有效^[7]。

1.2 分子内的 Heck 反应

载体上分子内的 Heck 反应主要优点是起始原料的假稀释效应能提高产率。第一个实例是 1995 年报道的从碘代芳烃(2.1)为起始原料合成 20-到 24-环的大环化合物(2.2)(见图 2)^[21]。此外, 使用 o-C-trityl 树脂(3.1)也可以合成 20-元环的化合物(3.2)(见图 3)^[22]。最近, 该方法已经应用于合成 15-元环的化合物库, 其中包括多种系列的氨基酸及多种不同大小的环^[23]。

表1 固载碘代芳烃和相关的化合物发生的分子间 Heck 反应

Table 1 Intermolecular Heck reactions on solid supports, polymer bound aryl iodides and related compounds

序号	起始原料	烯烃化合物	产品	反应条件	参考文献
1		$\text{CH}_2=\text{CHCO}_2^t\text{Bu}$ 	 Cleav: HCl , HTF , ultrasound, 50°C , 5min or HSiCl_3 , DCM , 32°C , 10min	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , DMF , ultrasound, 80°C , 24h	8, 9
2		$\text{CH}_2=\text{CHCO}_2\text{Et}$	 Cleav: (1) $\text{Et}_3\text{O}^+\text{BF}_4^-$; (2) $\text{PhB}(\text{OH})_3$, $\text{PdCl}_2(\text{dppf})$, K_2CO_3 , THF , 60°C , 14h	$\text{Pd}(\text{OAc})_2$, PPh_3 , K_2CO_3 , DMF , 70°C , 14h	10
3		alkene	 a $\text{R}^1 = \text{CO}_2^t\text{Bu}$, $\text{R}^2 = \text{R}^3$ (69%) b $\text{R}^1 = \text{SO}_2\text{Me}$, $\text{R}^2 = \text{R}^3$ (43%) c $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{R}^3 = \text{H}$ (NA) d $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{Ph}$ (NA) e $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$ (NA) MeONa (6 equiv), $\text{MeOH}/\text{dioxane}$ (v/v 1:4), 24h	AcONa , $n\text{Bu}_4\text{NCl}$, $\text{Pd}(\text{OAc})_2$, DMA , 100°C , 24h	11
4	 Tentagel-OH	$\text{CH}_2=\text{CHCO}_2\text{Et}$	 Cleav: $\text{THF}/\text{DCM}/\text{PhOMe}$ (50: 47:3)	$\text{Pd}(\text{AcO})_2$, PPh_3 , Bu_3NCl sat. K_2CO_3 , $\text{DMF}/\text{H}_2\text{O}$ (9:1), 37°C , 4h	12
5		$\text{CH}_2=\text{CHCO}_2\text{Et}$	 50%THFin DCM	$\text{Pd}_2(\text{dba})_3$, Et_3N , DMF , 60°C , 18h (DMF volume, 2 ~ 1mL/g of resin)	13
6		$\text{CH}_2=\text{CHCO}_2^t\text{Bu}$		$\text{Pd}(\text{OAc})_2$, $\text{P}(\text{o-tol})_3$, Et_3N , $\text{DMF}/\text{o-xylene}$, MW , 100°C	14
7		$\text{CH}_2=\text{CHCO}_2\text{Et}$	 NaOMe, THF	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , DMF	15

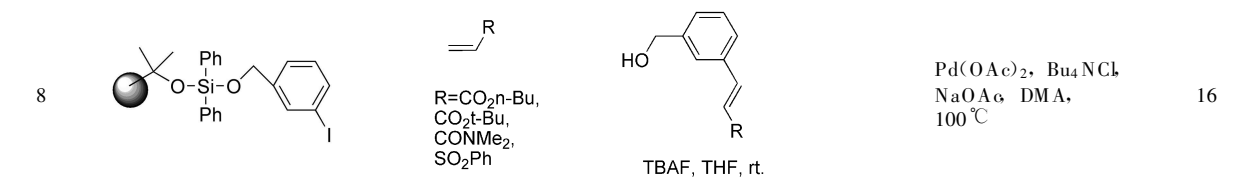
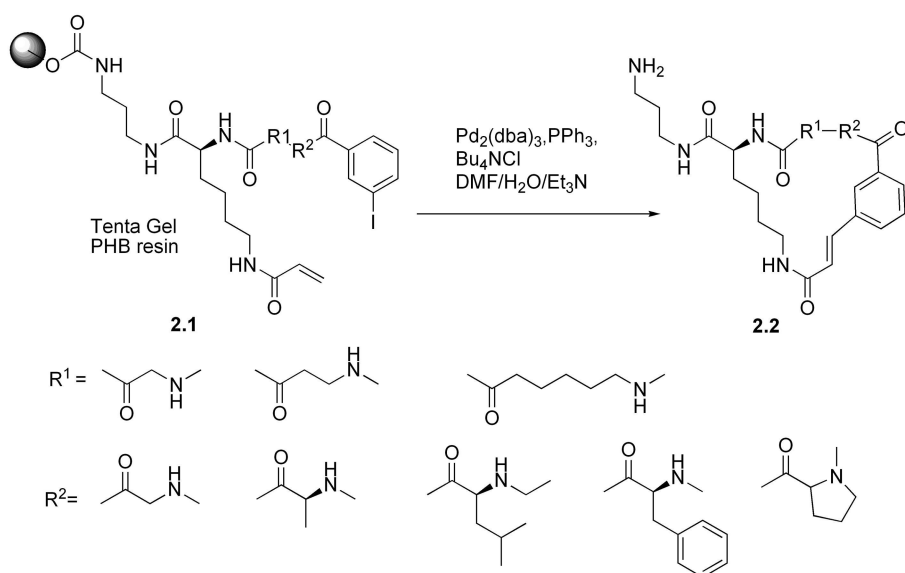


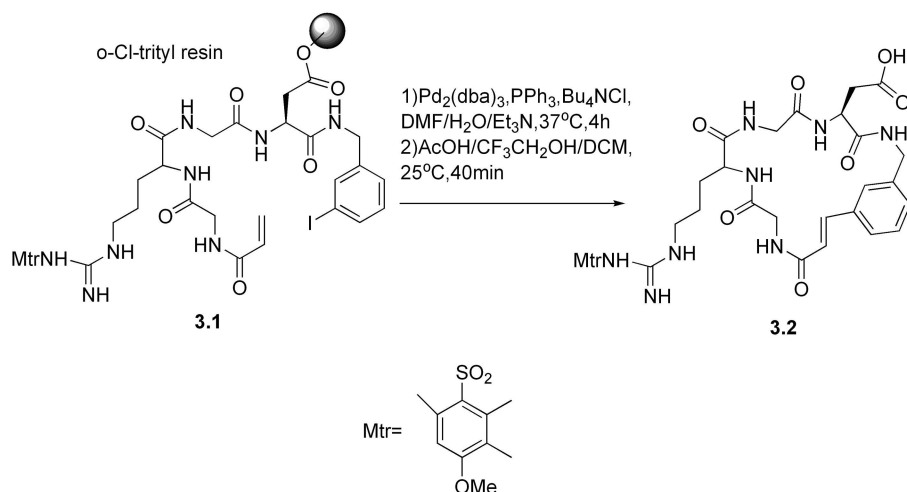
表 2 固载烯烃发生的分子间 Heck 反应

Table 2 Intermolecular Heck reactions on solid support: polymer-bound alkenes

序号	起始原料	卤代芳烃或碘盐	产品	反应条件	参考文献
1	 Wang resin	$\text{RX} = \text{PhI}$ 2-naphthyl-Br, 2-thienyl-Br, 3-Pyr-Br	 Cleav: 20% TFA, DCM, rt, 1h	$\text{Pd}_2(\text{dba})_3, \text{P}(\text{o-tol})_3,$ $\text{Et}_3\text{N}, \text{DMF}, 100^\circ\text{C},$ 20h or $\text{Pd}(\text{OAc})_2,$ $\text{Et}_3\text{N}, \text{n-BuNCl}, \text{DMF},$ $80 \sim 90^\circ\text{C}, 16\text{h}$	17
2	 MeO-PEG5000 $\text{R} = \text{o-MeOC}_6\text{H}_4, 1\text{-Naphthyl},$ $\text{o-Tol}, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-Pyr}, \text{cPr}$	$\text{ArI}; \text{Ar} = \text{p-Tol},$ $\text{p-BuC}_6\text{H}_4,$ $\text{p-MeOC}_6\text{H}_4$	 $\text{Z/E} < 1/99 \text{ to } 99/1$	$\text{Pd}(\text{OAc})_2, \text{NaHCO}_3,$ $\text{DMF}, 145^\circ\text{C}, 20\text{h}$	18
3		$\text{ArX}; \text{Ar} = \text{Ph},$ $\text{o-H}_2\text{NC}_6\text{H}_4,$ $\text{o-HOC}_6\text{H}_4$		$\text{Pd}_2(\text{dba})_3, \text{P}(\text{o-tol})_3,$ $\text{Et}_3\text{N}, \text{DMF},$ $40 \sim 100^\circ\text{C}, 20\text{h}$	19
4	 REM resin		 Cleav: NaOMe, MeOH, THF	$\text{Pd}_2(\text{dba})_3, \text{P}(\text{t-Bu})_3,$ $\text{DIPEA}, \text{super}$ critical CO_2 $(880\text{ps}), 80^\circ\text{C}, 16\text{h}$	20

图 2 分子内 Heck 反应合成大环化合物^[21]Figure 2 Intramolecular Heck reaction for the synthesis of macrocycles^[21]

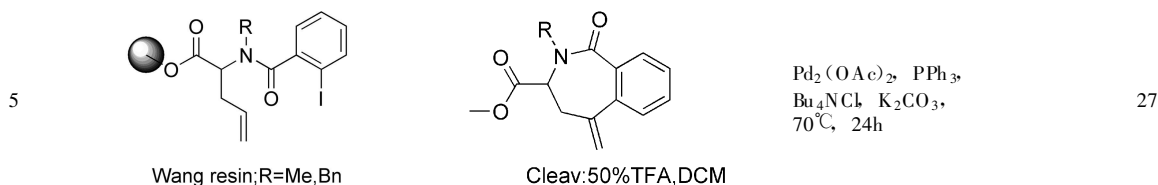
除了大环合成, 5、6、7-元环的杂环化合物的合成也有报道, 此外还有合成吡啶、苯并咪唑、二氢异喹

图3 分子内 Heck 反应合成大环化合物^[21]Figure 3 Intramolecular Heck reaction for the synthesis of a macrocycle^[22]

啉和苯并氮杂 类化合物的报道。合成上述化合物一般用负载的碘代芳烃和相应的烯醚或炔醚反应后,再进行还原和环合(见表3)。

表3 固相载体上钯催化合成吡啶、苯并呋喃、二氢异喹啉和苯并氮杂 类化合物

Table 3 Synthesis of indoles benzofurans dihydroisoquinolines and benzazepines by Heck reactions on solid supports				
序号	起始原料	产品	反应条件	参考文献
1	Rink amide or Rink amide resin	R=H,5,7-(Cl)₂; cleav:30%TFA,DCM	$\text{Pd}_2(\text{dba})_3$, CHCl_3, $\text{P}(\text{o-Tol})_3$, NaHCO_3, DMF, 40 °C, 20h	24
2	$\text{R}^1=\text{H}, \text{CH}_2\text{CH}_2\text{Hex}, \text{tBu}$; $\text{R}^2=\text{H}, \text{CH}_3, \text{Ph}$	Cleav:25%TFA,DCM,25°C,16h	$\text{Pd}_2(\text{OAc})_2$, PPh_3, Ag_2CO_3, DMF, 100 °C, 16 h	25
3	polystyrene with additional base-labile linker:R=CO₂Me,Ts,Ac	Cleav:MeONa, MeOH/dioxane(1:4), rt,24h	$\text{Pd}_2(\text{OAc})_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 100 °C, 24h	26
4	polystyrene with additional base-labile linker:R=CO₂Me,Ts,Ac	Cleav:MeONa, MeOH/dioxane(1:4), rt,24h	$\text{Pd}_2(\text{OAc})_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 100 °C, 24h	26



1.3 载体上多组分的 Heck 反应

载体上的多组分 Heck 反应尤其适合于组合合成。Wang 等报道了非共轭二烯(4.2)同时与卤代芳烃(4.3)以及负载在 Rink 树脂上的胺基化合物(4.1)三组分固相反应合成了 4.4(见图 4)^[28]。同以卤代芳烃作为载体的 Heck 反应相比较,该反应的优点在于反应过程产生的二组分 Heck 反应产物及来自于负载卤代芳烃的可能副产被留在溶液里可以通过洗涤方便地除去。该三组分反应产率可以达到 70%~95%,产品 4.4 的纯度也比较满意。该方法能灵活的应用于不同起始原料,因此很受欢迎。

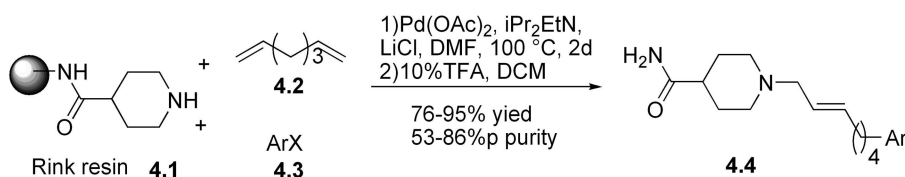


图 4 固相载体连接的哌啶同 1,5-己二烯和卤代芳烃的偶联反应^[28]

Figure 4 Coupling of a solid-supported piperidine with 1,5-hexadiene and aryl halides^[28]

2 聚合物载体上的 Negishi 反应

Negishi 偶联反应即锌酸盐参与的交叉偶联反应。SPOS 条件下的 Negishi 反应是将卤代芳烃连接在聚合物载体上(大多数情况下是卤代芳烃或者磺酰酯)和锌盐反应或者是将锌盐固定在载体和可溶性的卤代芳烃反应(见表 4)。含杂原子芳环有机锌盐与卤代芳烃的交叉偶联反应可以制备含杂原子的双芳烃化合物。该反应的特点是锌酸盐对大多数官能团无影响,况且锌酸盐可以由格氏试剂或芳基锂化合物方便地制备。聚合物负载的溴代芳烃 5.1^[29](见图 5)、碘代芳烃 6.1、三氟甲磺酸取代芳烃 6.3(见图 6)^[30]等与各种锌酸盐偶联,经切割后分别得到酯 5.2 和羧酸 6.4。最近报道了由相应的碘代芳烃 7.1 与特丁基锌酸盐反应原位制备负载芳基锌酸盐,并与卤代芳烃缩合^[31]。由咪唑 8.2 合成的聚合物负载咪唑基锌盐形成负载的芳基咪唑切割后得到羟基咪唑 8.3(见图 8)^[32]。

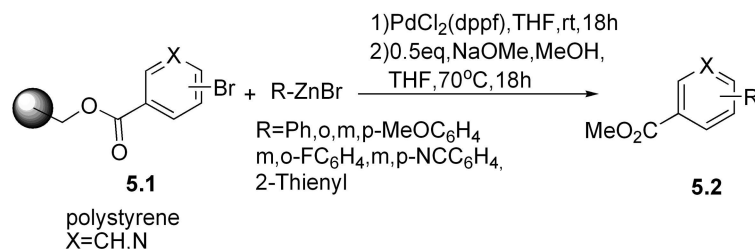
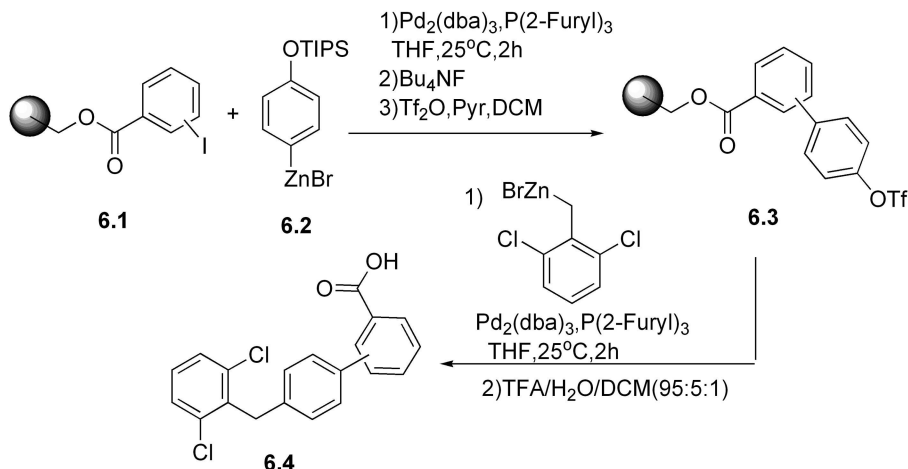
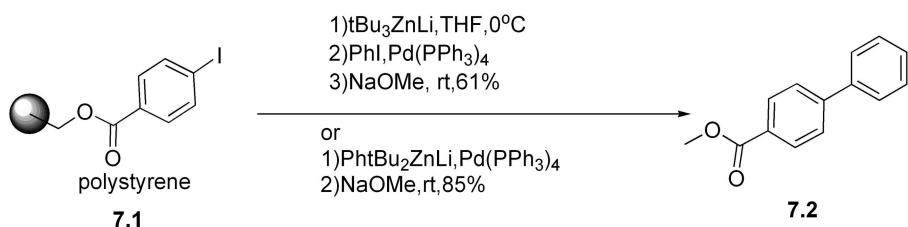
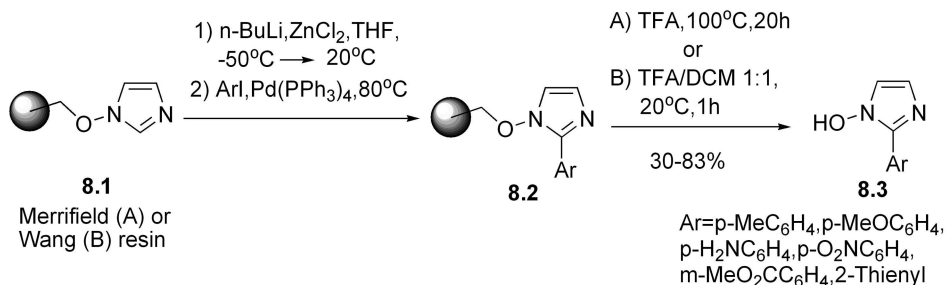


图 5 固载溴代芳烃发生的芳基-芳基偶联反应^[29]

Figure 5 Aryl-Aryl cross-coupling reaction with polymer-bound aryl bromides^[29]

图6 固载碘代芳烃和三氟磺酸酯芳烃发生的芳基-芳基偶联反应^[30]Figure 6 Aryl-aryl cross-coupling reaction with polymer-bound aryl iodides and triflates^[30]图7 固载芳烃锌盐发生的芳基-芳基偶联反应^[31]Figure 7 Aryl-aryl cross-coupling reaction with polymer-bound arylzineates^[31]图8 固载咪唑锌盐发生的芳基化反应^[32]Figure 8 Arylation of a polymer-bound imidacylzincate^[32]

3 聚合物载体上 Suzuki 偶联反应

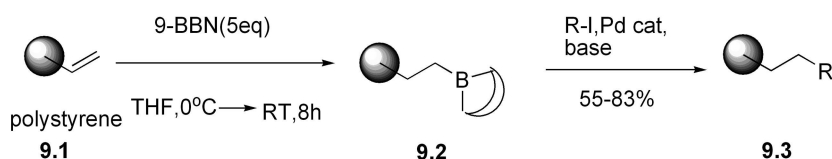
Suzuki 反应是钯催化的卤代芳烃与芳香硼酸(酯)之间的偶联反应^[38]。近些年,该方法已经广泛应用于烷基、烯丙基、烯基、炔基卤代物同温和的烷基硼试剂反应。由于该反应的反应条件温和,能同多种官能团兼容且起始原料(硼酸)易得,使这类反应变成了固相合成的一种强有力工具。同其它偶联反应相比, Suzuki 反应一般无毒并且硼酸对热、空气和湿度都稳定。

负载在树脂上的乙烯 9.1 用 9-BBN 硼氢化得到单个苯硼烷试剂 9.2 (见图 9), 该中间体可以和多种功能基的碘代芳烃、碘代烯、碘代烷烃偶联产生带氨基、酯基和被保护羟基官能团化合物^[39]。同样,也可以将溴代聚苯乙烯和功能基化硼烷偶联得到易处理的含功能基的负载化合物,例如硅无痕迹连接树脂(见表 5, 16, 17)^[51]。

表 4 固载芳基锌盐或者固载芳基卤和三氟磺酸盐发生的 Negishi 反应

Table 4 Negishi reactions with immobilised zinc salt or with immobilised aryl halides and triflates

序号	起始原料	卤代芳烃或锌盐	产品	反应条件	参考文献
1		(Het)ArX= PhI, 2-Br-Py, PhBR	 Cleav: MeOCOCI(3eq) rt, 3h	PPh ₃ , DMF, reflux, 18h	33
2		A rZnX Ar= Ph, 3-MeO-C ₆ H ₄	 TFA/DCM 1:1 MW, 160°C, 5min	Pd ₂ (dba) ₃ , tBu ₃ P, HBF ₄ MW, THF/NMP 175°C, 10min	34
3				Ni(PPh ₃) ₂ Cl ₂ , PPh ₃ , LiCl, THF, reflux, 48h	35
4				Pd(PPh ₃) ₄ , dry THF, N ₂ , rt, 24h	36
5		RZnX(5eq) R= Ph, Ar, Bn, Alkyl	 50% TFA/DCM	(PPh ₃) ₄ , THF, 65°C, 18h	37

图 9 硼烷衍生化反应^[39]Figure 9 Derivatisation of a borane^[39]

如果用碘代芳烃, 偶联反应可以用 Pd(OAc)₂ (0.3 eq)、PPh₃ (0.9 eq)、NaOH (3 eq)、相转移催化剂 (Triton B, 1.5 eq) 和碘化物 (4 eq) 在 DMF 中 85 °C 反应 14h。碘代的烯基和烷基可以用 PdCl₂(dppf) 作为催化剂 K₂CO₃ 作为碱进行偶联。微波促进芳基硼酸或杂环硼酸同聚合物的溴代或碘代苯甲酸的偶联反应能在温和条件下短时间内反应完成 (4min, 40W)^[60]。

用双硼酸酯和聚合物负载的碘代芳烃在钯催化下反应可以得到相应的聚合物负载的硼酸酯 (见表 5, 6, 7), 然后再与各种卤代芳烃进行 Suzuki 偶联反应从载体上切割后能高产率高纯度得到多种连二芳烃的化合物 (见表 5, 2, 5)。

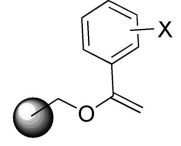
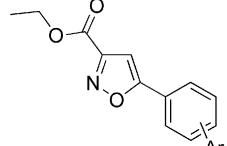
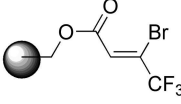
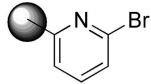
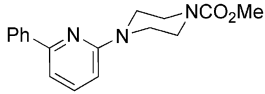
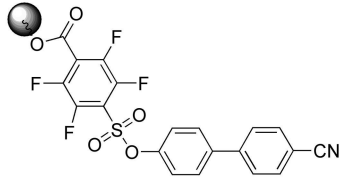
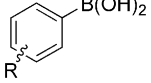
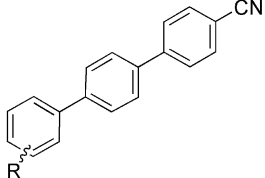
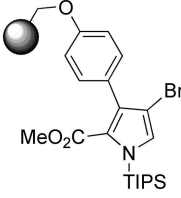
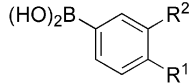
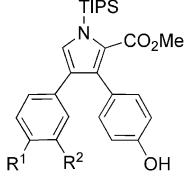
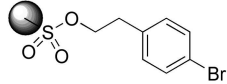
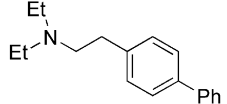
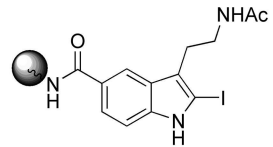
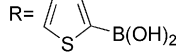
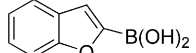
表 5 固载卤代芳烃、卤代烯烃和三氟磺酸酯发生的 Suzuki 反应

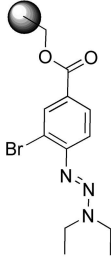
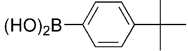
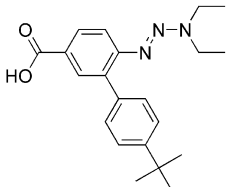
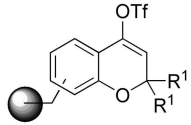
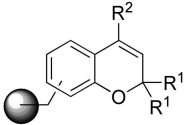
Table 5 Suzuki reactions with immobilised aryl or alkenyl halides and triflates

序号	起始原料	芳基和烯烃 硼烷/硼酸	产品	反应条件	参考文献
1		$\text{RB}(\text{OH})_2$	 a R=4-(Methylthio)-phenyl b R=4-methoxyphenyl MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.	K_2CO_3 , $\text{Pd}(\text{OAc})_2$, dioxane, H_2O 100°C , 20h	11
2		$\text{ArB}(\text{OH})_2$		$\text{PdCl}_2(\text{dppf})$, Et_3N , DMF, 65°C , 24h	40
3		$\text{ArB}(\text{OH})_2$		$\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , DMF, 70°C	41
4		$\text{ArB}(\text{OH})_2$		$\text{Pd}(\text{PPh}_3)_4$, K_2PO_4 , DMF, 80°C , 24h 50%TFA in DCM	42
5		$\text{ArB}(\text{OH})_2$		$\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , tol/EtOH (8:1), 90°C , 24h $\text{R}^1=\text{H}$ yield>75% $\text{R}^1=\text{alkyl}$ 50%TFA in DCM	42
6				$\text{Pd}(0)$, KOAc, DMSO, 80°C , 2h	43
7				$\text{PdCl}_2(\text{dppf})$, KOAc, DMF, 80°C , 16h	44

8				$\text{Pd(PPh}_3)_4$ K_3PO_4, $\text{THF/H}_2\text{O (6:1)}$, 80°C, 2d NIS, HF/Py, DCM, $-78^\circ\text{C}-0^\circ\text{C}$, 3h	45
9				$\text{Pd(PPh}_3)_4$ K_3PO_4, $\text{THF/H}_2\text{O (6:1)}$, 80°C, 2d NIS, HF/Py, DCM, $-78^\circ\text{C}-0^\circ\text{C}$, 3h	45
10				$\text{Pd(PPh}_3)_4$ K_3PO_4, $\text{THF/H}_2\text{O (6:1)}$, 80°C, 2d NIS, HF/Py, DCM, $-78^\circ\text{C}-0^\circ\text{C}$, 3h	45
11		ArB(OH)_2		$\text{Pd(PPh}_3)_4$ $2\text{M Na}_2\text{CO}_3$, $\text{Xylene/H}_2\text{O (6:1)}$, 80°C, 24h MeONa MeOH/THF	46
12		RB(OH)_2		$\text{Pd(PPh}_3)_4$ K_3PO_4, 55°C TFA/H₂O (95:5).	47
13		ArB(OH)_2		Pd(dppf)Cl_2, K_3PO_4, $\text{toluene/t-BuOH/H}_2\text{O}$ $9:9:1$, 85°C, 4h 0.1M NaOH(aq)	48

14		RB(OH)_2		cat., Pd(OAc)_2 , $\text{PPh}_3\text{C}_6\text{F}_5$, DME, 4h, 90°C	49
15				$\text{Pd(PPh}_3)_4$, Na_2CO_3 , DMF/ H_2O (90/10), 80°C , 16h	50
16		9BBN		$\text{Pd(PPh}_3)_4$, Na_2CO_3 , DMF, 75°C , 48h	51
17		9BBN		$\text{Pd(PPh}_3)_4$, K_3PO_4 , DMF, 75°C , 48h	51
18		PhB(OH)_2		$\text{Pd(PPh}_3)_4$, Na_2CO_3 , DMF, 75°C , 48h	52
19		ArB(OH)_2 ; $\text{Ar} = \text{Ph}$, o-MeC ₆ H ₄ , p-F ₃ CC ₆ H ₄		$\text{Pd(PPh}_3)_4$, Na_2CO_3 , DMF/ H_2O 15:1, 80°C , 45h	53
20		$(\text{HO})_2\text{B}$		$\text{Pd(PPh}_3)_4$, $\text{P}(\text{t-Bu})_3$, CS_2CO_3 , DMF, 80°C , 4h	54
21		ArB(OH)_2 ; $\text{Ar} = \text{p-OHCC}_6\text{H}_4$, m-O ₂ NC ₆ H ₄ , m-NHAcC ₆ H ₄ , p-HO ₂ CC ₆ H ₄ , p-NCC ₆ H ₄ , m-(F ₃ C) ₂ C ₆ H ₃ , 3-Thienyl		Pd(OAc)_2 , dppf, CS_2CO_3 , DMF, 90°C , 16h	55

- 22  Wang or Merrifield resin: X=m-l, p-Br
1) ArB(OH)₂: Ar= p-OHCC₆H₄, m-O₂NC₆H₄, m-NHAcC₆H₄, p-HO₂CC₆H₄, p-NCC₆H₄, m-(F₃C)₂C₆H₃, 3-Thienyl
2) ethyl chloroimidate, NEt₃, THF, 1h, four times
 Cleav: 3% TFA, DCM, 25°C, 30min
Pd(OAc)₂, dppf, Cs₂CO₃, DMF, 90°C, 16h 55
- 23  ArB(OH)₂: Ar= phenyl, m-O₂NC₆H₄, m-MeOC₆H₄, p-FC₆H₄, p-MeOC₆H₄, p-MeSC₆H₄, m-EtOC₆H₄, 3-Thienyl
Cleav: MeONa in MeOH/THF (1:4), followed by flash chromatography
Pd(PPh₃)₄, Na₂CO₃, Xylene/ EtOH, 80°C, 24h 56
- 24  PhB(OH)₂
 Cleav: MeOCOC(3eq), DCM, rt, 3h
PbCl₂(PPh₃)₂, CuI, K₂CO₃, DMF, reflux, 18h 33
- 25    Pd(dppf), K₂CO₃, THF/ H₂O, reflux, 48h 35
- 26  (HO)₂B-   Na₂CO₃, Pd(PPh₃)₄, dioxane, reflux, 48h 36
AlCl₃, dry DCM, rt, 3 h.
- 27  p-MeC₆H₄B(OH)₂
polystyrenen with spacer
 Cleav: Et₂NH, 60°C, 18h
Pb(PPh₃)₄, K₂CO₃, toluene, EtOH, 90°C, 20h 57
- 28  RB(OH)₂
R=  B(OH)₂,  B(OH)₂
K₂CO₃, Pd(OAc)₂, dioxane, H₂O (6:1), 110°C, 21 ~ 48h 58

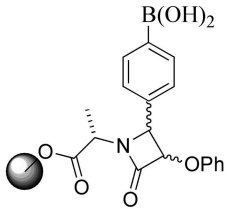
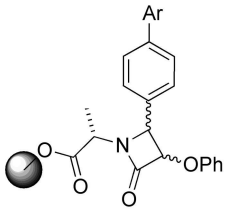
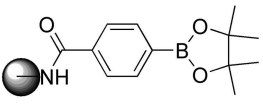
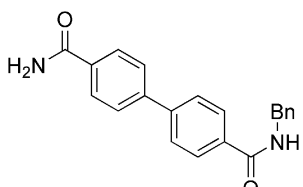
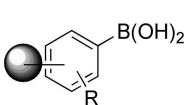
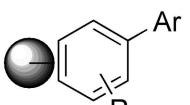
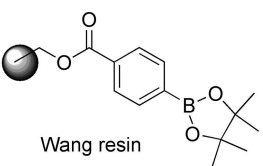
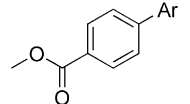
29				$\text{PbCl}_2(\text{PPh}_3)_2$, Na_2CO_3 , H_2O	15
30		$\text{R}^2\text{B}(\text{OH})_2$ $\text{R}^2 = 4\text{-chloro-2-methylphenyl}$, 4-fluorophenyl		$\text{Pb}(\text{PPh}_3)_4$, Na_2CO_3 , $1,4\text{-dioxane}/\text{H}_2\text{O}$	59

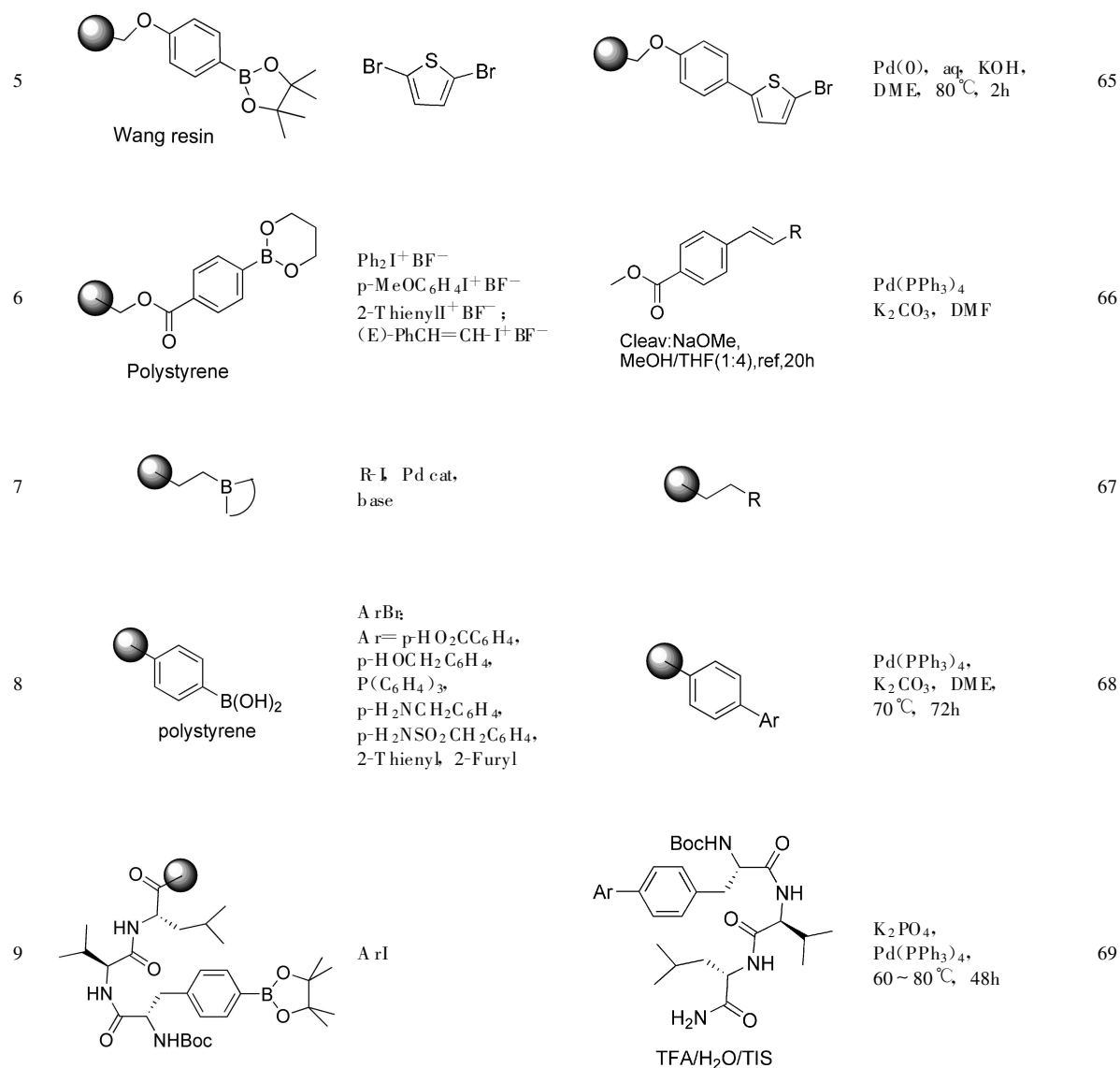
用负载的碘苯和苯硼酸偶联研究了聚苯乙烯树脂交联度和聚苯乙烯树脂交联度对反应速率的影响(表 5, 18)^[52]。正如所预测的一样, 在低交联度树脂(0.3% DVB)上偶联过程反应速率比在高交联度树脂(2.7% DVB)上快 11 倍, 但是有研究人员观察到用 3.0% 和 6.0% DVB 交联的树脂载体上得到偶联产品的产率只有 3%~5%, 这主要归因于较大的 $\text{Pd}(\text{PPh}_3)_4$ 分子不能有效接近反应位点进行催化。

一般情况下, 用聚合物负载卤代芳烃(见表 5)比聚合物负载硼酸(见表 6) Suzuki 反应更易成功。最近的一个报道描述了使用负载的苯硼酸与负载的卤代芳烃通过树脂间的 Suzuki 偶联反应^[61]。

表 6 聚合物负载芳基硼试剂和烯基硼试剂发生的 Suzuki 反应

Table 6 Suzuki reactions with polymer bound aryl and alkyl boranes

序号	起始原料	卤代芳烃	产品	反应条件	参考文献
1		ArI		$\text{PdCl}_2(\text{dppf})$, Et_3N , H_2O , 40°C , 24h	40
2	 Rink amide	p-IC ₆ H ₄ CONHBn	 Cleav: 30% TFA, DCM	$\text{Pd}(\text{PPh}_3)_4$, DMF, 70°C	62
3		ArI		$\text{Pd}(\text{PPh}_3)_4$, EtOH, K_2CO_3 , toluene, ref, 12h	63
4	 Wang resin	ArX: Ar = Ph, $\sigma\text{-NO}_2\text{C}_6\text{H}_4$, $m\text{-MeOC}_6\text{H}_4$, $\sigma\text{-NCC}_6\text{H}_4$	 Cleav: 1) 50% TFA, DCM, 3min 2) Me ₃ SiCHN ₂ , CHCl ₃ , MeOH	$\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , DMF	64



2006 年, 作者的研究小组使用 Suzuki 交叉偶联反应把 BINOL 键合到树脂载体上 (见图 10) 催化苯基甲基硫醚的手性氧化反应 (见图 11) 并获得较好效果。^[70]

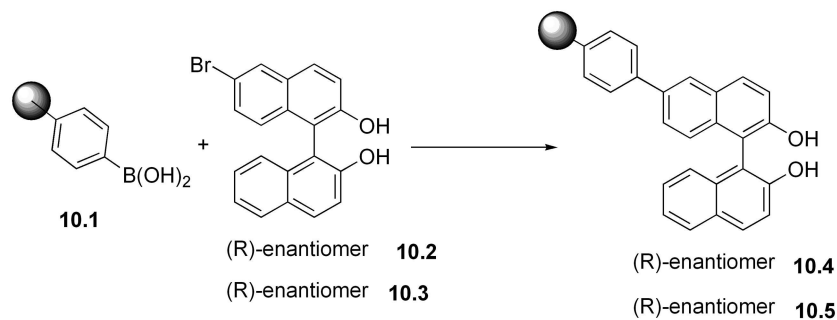
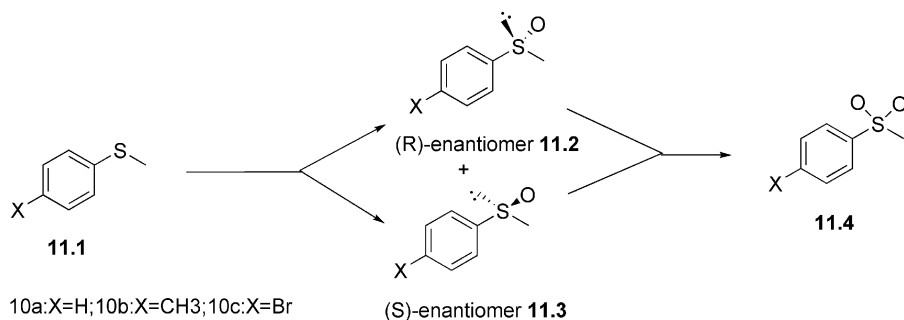


图 10 用于制备 PS 手性 BINOLs 的反应^[70]

Figure 10 Reaction used to prepare PS chiral BINOLs^[70]

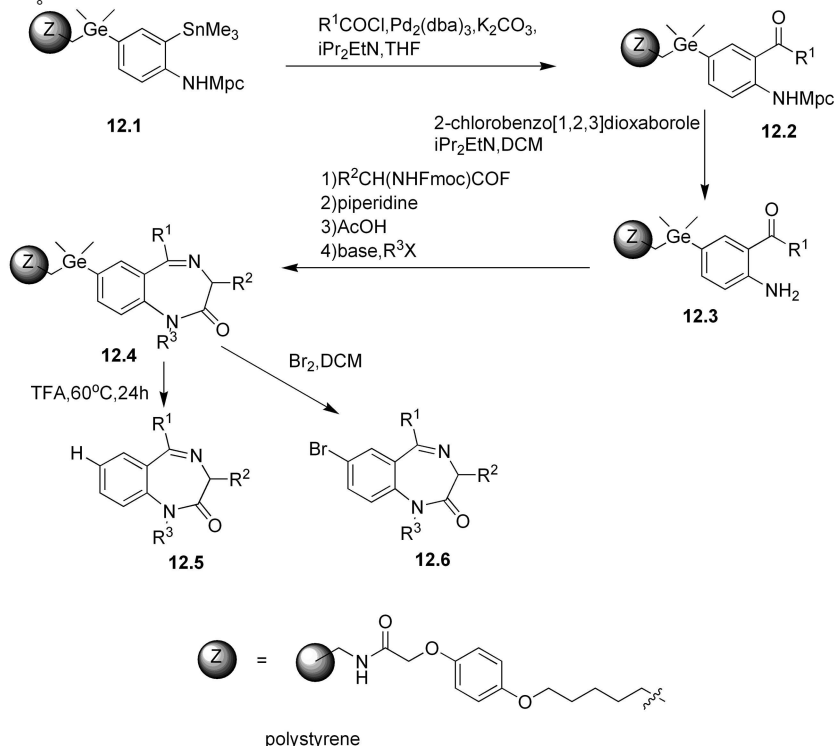
图 11 芳基甲基硫醚的氧化反应^[70]Figure 11 Oxidation of aryl methyl thioethers^[70]

4 聚合物载体上的 Stille 偶联反应

在这里我们有必要提及美国科罗拉多州立大学化学系 John K. Stille 教授提出的 Stille 偶联反应^[71], 该反应是第一个由小分子移植到固相载体上进行的交叉偶联反应^[72]。

使用钯催化的芳基锡、烯基锡、炔基锡与芳基溴、芳基碘或三氟甲磺酰基取代的芳香族化合物进行的 Stille 偶联反应的反应条件与相应的液相反应相类似, 并要加入砷或三咪唑基膦作为配体。由于在处理均相反应时分离无机锡盐和有机锡试剂或副产物的单调乏味, 使用聚合物载体进行该反应有特殊意义。遗憾的是 John K. Stille 已于 1989 年死于空难, 因而未能获得这次诺贝尔化学奖, 但是他的名字也应该和这次获诺贝尔化学奖的 3 位科学家一样载入史册。

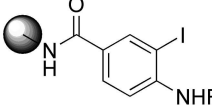
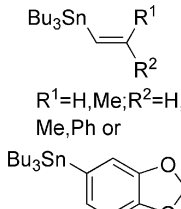
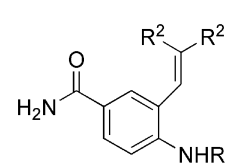
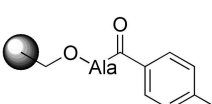
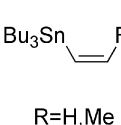
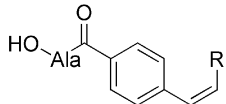
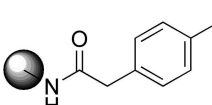
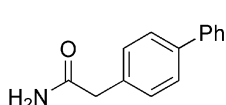
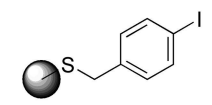
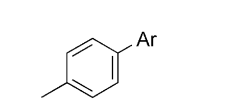
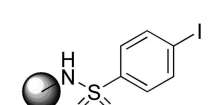
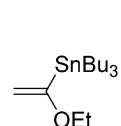
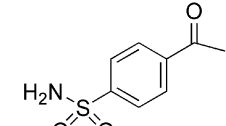
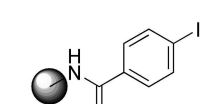
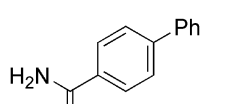
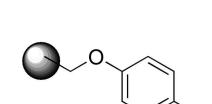
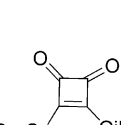
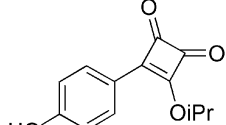
固载的卤代芳烃与芳基锡和烯基锡的 Stille 偶联反应已经得到广泛的应用(见表 7), 相比之下, 将锡试剂固载在聚合物载体上的 Stille 偶联反应则较少报道(见表 8), 但也已经用于 Ellman's 苯并二氮杂的合成(见图 12)^[94]。

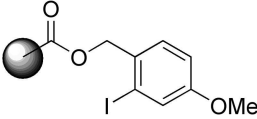
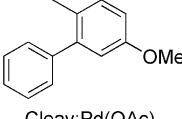
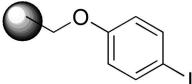
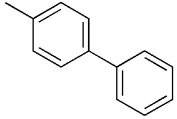
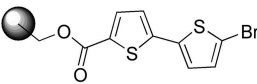
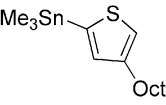
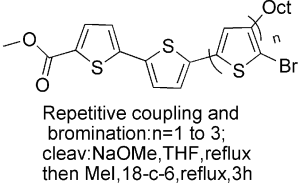
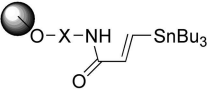
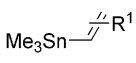
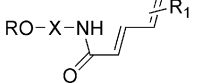
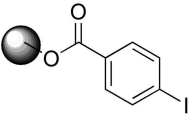
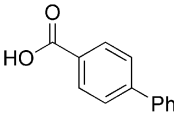
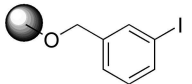
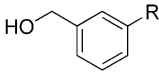
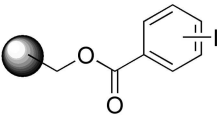
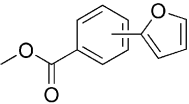
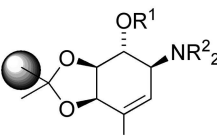
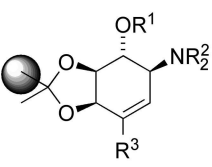
图 12 苯并二氮杂 的合成^[94]Figure 12 Synthesis of benzodiazepines^[94]

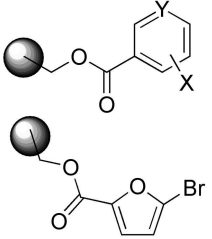
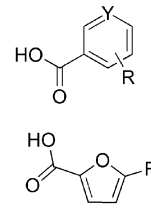
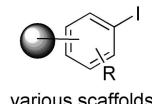
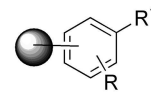
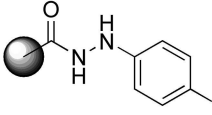
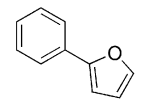
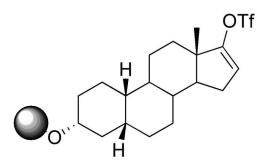
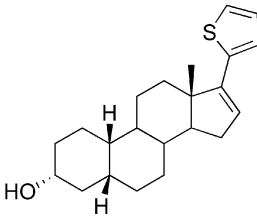
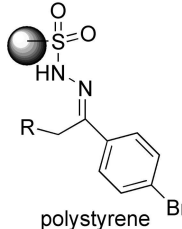
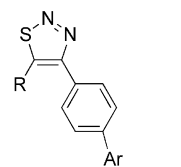
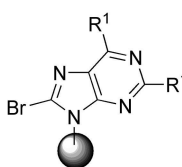
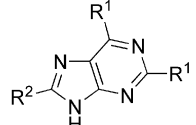
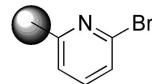
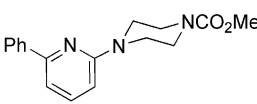
各种溴代芳烃和碘代芳烃大多能用于 Stille 反应, 该反应也能用于微波反应(见表 7, 6)。大家比较感兴趣的是 Stille 偶联反应能用多聚物连接卤代苯酯, 再经钯催化氢解切割, 在反应液中能方便得到高纯度的相应甲基取代芳烃(见表 7, 8)。

表 7 固载的卤代芳烃发生的 Stille 反应

Table 7 Stille reactions with immobilised aryl halides

序号	起始原料	锡试剂	产品	反应条件	参考文献
1	 Rink amide	 R ¹ =H, Me; R ² =H, Me, Ph or	 Cleav: 5% TFA, DCM	Pd ₂ (dba) ₃ , AsPh ₃ , NMP, 45 °C, overnight	72
2	 Wang resin	 R=H, Me	 Cleav: 95% TFA, DCM	Pd ₂ (dba) ₃ , AsPh ₃ , NMP, 45 °C, overnight	72
3	 Rink resin	Bu ₃ SnPh	 Cleav: 5% TFA, DCM	Pd ₂ (dba) ₃ , P(2-Furyl) ₃ , LiCl, NMP, rt, 12h	73
4	 Rink amide with NpSSMpack linker	Me ₃ SnAr; Ar= Ph, m- AcOC ₆ H ₄	 Cleav: hv(350nm), MeCN	Pd ₂ (dba) ₃ , P(2-Furyl) ₃ , LiCl, NMP, rt, 12h	73
5	 Rink amide		 Cleav: 20% TFA, DCM	Pd ₂ (dba) ₃ , AsPh ₃ , NMP, rt, 15h	74
6	 Rink amide Tentagel	Bu ₃ SnPh	 Cleav: 90% aq. TFA, 1h	Pd ₂ (dba) ₃ , AsPh ₃ , NMP, microwave irradiation (3-8 min, 40W)	75
7	 Wang resin		 Cleav: 20% TFA, DCM, rt, 20min	PdCl ₂ (PPh ₃) ₄ , CuI, DMF, rt, 30h	76

8		polystyrene with magnetite core			$\text{Pd}_2(\text{dba})_3$, $\text{P}(2\text{-Furyl})_3$, LiCl , NMP, 65°C , 22h	77
				Cleav: $\text{Pd}(\text{OAc})_2$, NH_4HCO_3 , DMF, 65°C , 20h		
9		polystyrene with thio linker and with magnetite core	Me_3SnPh		$\text{Pd}_2(\text{dba})_3$, $\text{P}(2\text{-Furyl})_3$, LiCl , NMP, microwave irradiation, 2h	77
				Cleav: $\text{hv}(350\text{nm})$, DMF, 6h		
10					$\text{PdCl}_2(\text{PPh}_3)_2$, LiCl , DMF, 80°C	78
				Repetitive coupling and bromination: $n=1$ to 3; cleav: NaOMe, THF, reflux then MeI, 18-c-6, reflux, 3h		
11		Wang or PEG: X=Gly, Phe, Ala-Aca, Arg(Pbf)-Aca			$\text{Pd}_2(\text{dba})_3$, AsPh_3 , NMP, 45°C , overnight	79
		various substituents		Cleav: R=H; TFA/DCM/ H_2O (80:15:5), rt, 1h; R=Me; DCM, MeOH, DBU, rt, overnight		
12		Tentagel S with photocleavable linker	Me_3SnPh		$\text{Pd}_2(\text{dba})_3$, AsPh_3 , NMP, 50°C , 42h	80
				Cleav: $\text{hv}(\text{Hg pressure}, >320\text{nm})$		
13		polystyrene with base labile linker	Bu_3SnR ; R= Aryl, Hetaryl or Alkenyl		$\text{Pd}_2(\text{dba})_3$, AsPh_3 , dioxane, 50°C , 24h (preferentially) or $\text{Pd}(\text{PPh}_3)_4$, dioxane, 100°C , 24h	81
				Cleav: 6 eq, NaOMe, MeOH/dioxane(1:4), rt, 24h		
14		polystyrene on SynPhase crown	$\text{Bu}_3\text{Sn}(2\text{-Furyl})$		$\text{Pd}_2(\text{dba})_3$, AsPh_3 , THF	72
				Cleav: 0.1M NaOMe, THF/MeOH(4:1), rt, 24h		
15		Wang type diol linker	Bu_3SnR^3 ; R^3 = various alk enyl groups		$\text{Pd}_2(\text{PPh}_3)_4$, dioxane, 100°C , 24h	

16	 polystyrene: Y=CH, H	Bu_3SnR ; R= Ph, Ethenyl, 2-Furyl, 2-Thienyl, $\sigma\text{-Et}_2\text{NC}(\text{O})\text{C}_6\text{H}_4$, $\sigma\text{-Et}_2\text{NC}(\text{O})\text{OC}_6\text{H}_4$		$\text{Pd}(\text{PPh}_3)_4$, DMF, 60 °C, 24 ~ 28h	84
17	 various scaffolds	R^1SnBu_3 ; R^1 = 2-Furyl, 2-Thienyl, 2-Pyr, 3-Pyr, Ethenyl		$\text{Pd}_2(\text{dba})_3$, AsPh_3 , dioxane, 50 °C, 24h	85
18	 polystyrene or TentaGel or ArgoPore	$\text{Bu}_3\text{Sn}(2\text{-Furyl})$	 Cleav: $\text{Cu}(\text{OAc})_2$, MeOH, pyr, rt, 2h	$\text{Pd}_2(\text{dba})_3$, AsPh_3 , dioxane, 60 °C, 24h	86
19	 polystyrene with fluoride-labile linker	$\text{Bu}_3\text{Sn}(2\text{-Thienyl})$	 Cleav: TABF, TMU, 100 °C, 1h	$\text{Pd}(\text{PPh}_3)_4$, LiCl, DMF, 110 °C, 3h	87
20	 polystyrene	Bu_3SnAr ; Ar= Ph, p-F- C_6H_4	 Cleav: SOCl_2, $\text{ClCH}_2\text{CH}_2\text{Cl}$ 60 °C, 5h	$\text{PdCl}_2(\text{PPh}_3)_2$ DMF, 90 °C, 24h	88
21		R^2SnBu_3 ; R^2 = Ph, 2-Furyl, $\text{C}(\text{OEt})\text{CH}_2$, 2-Pyr, CCPh , m-EtOC $_6\text{H}_4$, Ethenyl	 Cleav: 20% TFA, $\text{ClCH}_2\text{CH}_2\text{Cl}$	$\text{Pd}(\text{OAc})_2$, dppp, Cu_2O , NMP, 100 °C, 20h	89, 90
22		PhSnBu_3	 Cleav: MeOCOCI (3eq), DCM, rt, 3h	$\text{PbCl}_2(\text{PPh}_3)_2$, DMF, reflux, 18h	33

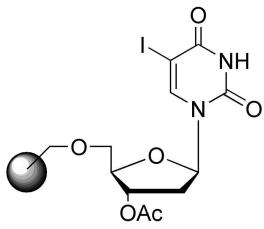
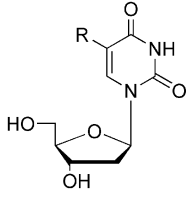
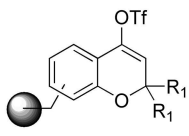
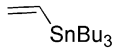
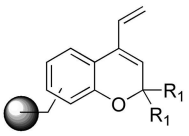
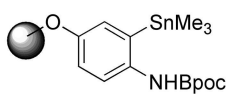
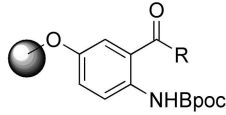
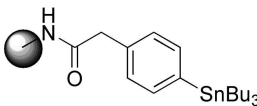
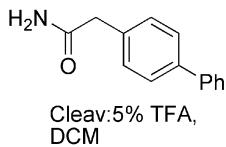
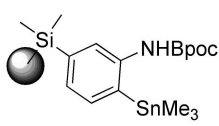
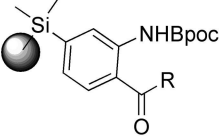
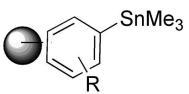
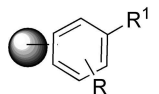
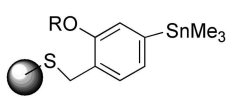
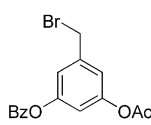
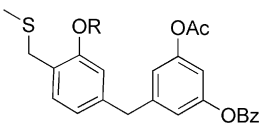
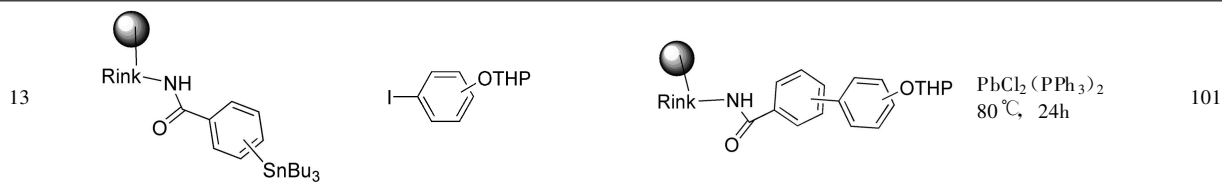
23		R^1SnR^2_3		CuI , Ph_3As , $\text{Pd}_2(\text{dba})_3$, dioxane, 80°C , 20h	11
			a R=4-(Methylthio)-phenyl b R=4-methoxyphenyl MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.		
24				$\text{Pd}(\text{PPh}_3)_4$, 1, 4-dioxane	59

表 8 聚合物负载锡试剂发生的 Stille 反应

Table 8 Stille reaction with polymer-bound stannanes

序号	起始原料	亲电试剂	产品	反应条件	参考文献
1	 polystyrene with linker	RCOCl ; R= α -m, p-MeOC ₆ H ₄ , cHex, 2-MeNCC ₆ H ₄ , m-CF ₃ C ₆ H ₄ , p-tBuC ₆ H ₄ , o-ClC ₆ H ₄ , 1-(p-ClPh)cPent, CH ₂ CH ₂ CO ₂ Me, Thienyl, 2-Furyl, 1-Ad, 2-Naphthyl, 3-(1,2-methylene-dioxo)C ₆ H ₃		$\text{Pd}_2(\text{dba})_3$, CHCl ₃ , K ₂ CO ₃ , HTF, rt	91, 92
2	 Rink amide	PhI or PhOTf	 Cleav: 5% TFA, DCM	$\text{Pd}_2(\text{dba})_3$, TFP, LiCl, NMP, rt, 12h	93
3	 polystyrene with linker	RCOCl ; R= m, p-MeOC ₆ H ₄ , 1-Ad, Ph		$\text{Pd}_2(\text{dba})_3$, CHCl ₃ , K ₂ CO ₃ , THF, iPr ₂ NH, rt	94
4		$\text{R}^1=\text{X}$; $\text{R}^1\text{X}=\text{ArOTf}$, ArCH_2Br		$\text{PdCl}_2(\text{PPh}_3)_2$, LiCl, DMF, 120°C , 28h	63
5	 Tentagel			$\text{Pd}(\text{PPh}_3)_4$, Et ₃ N, reflux, 4h	63

- | | | | | | |
|----|--|---|--|---|-----|
| 6 | | RCOCl; R= m, p-MeOC ₆ H ₄ , 1-Ad, 3-(1,2-methylene-dioxo)C ₆ H ₃ , 2-Naphthyl | | Pd ₂ (dba) ₃ , CHCl ₃ , K ₂ CO ₃ , THF, rt, 1h | 95 |
| 7 | | R=H,OMe
polystyrene with linker | | Pd(PPh ₃) ₄ , aq. Na ₂ CO ₃ , DME, reflux, 12h | 96 |
| 8 | | RBr; R= 2-, 3-Py r, Ph, 2-Thienyl and other hetaryl | | Pd(PPh ₃) ₄ , LiCl, DMF, 100 °C | 97 |
| 9 | | ArX; X= Br, I | | Palladacycle
LiCl, NMP, 90 °C | 98 |
| 10 | | ArX | | Pd(PPh ₃) ₄ , 3,5-di-tBu-4-hydroxy-toluene, toluene, N ₂ , 90 ~ 100 °C, 24h | 99 |
| 11 | | | | Pd ₂ (dba) ₃ , AsPh ₃ , CsF, DMF, 80 °C, 12h | 100 |
| 12 | | (Het)ArX= PhI, 2-Br-Py, PhBr | | PPh ₃ , DMF, reflux, 18h | 33 |



5 结 论

尽管钯催化的交叉偶联反应在固相合成中已经获得可喜可贺的成绩,但是在一些其它的催化反应方面,如用手性配体控制立体化学等还未得到广泛的研究。到目前为止,所获得大部分化合物库只是包含外消旋的和通常是非对映异构体的混合物,因此高选择性合成单一构型的手性化合物将是固相组合化学合成中的下一个挑战。

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Research Progress of Pd Catalyzed Cross-coupling Reactions Utilized in Solid Phase Organic Synthesis

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Abstract: Coupling reaction using transition metal Pd as catalyst has been very efficient in formulating C-C bond, thus Pd catalyzed C-C coupling reaction has been under spotlight of scientists' attention for years and series of derivative reactions were thence developed, among which Pd catalyzed Solid-phase organic reactions such as Heck reaction, Negishi reaction, Suzuki coupling and Stille coupling, with their accessible reaction conditions, high tolerance of diverse functional groups, low steric hindrance, excellent chemical selectivity, mild toxicity, side products friendly and removable, efficient in yields, have always been the researching focus of catalytic chemistry and solid phase combinatory chemistry. With reference to different classification standards and our own research work, this article reviews the researching progresses of Pd catalyzed Cross-coupling reactions used in solid phase organic synthesis reactions, such as Heck/Negishi/Suzuki and Stille reaction.

Key words: Palladium catalyzed cross-coupling reactions; Heck reaction; Negishi reaction; Suzuki coupling; Stille coupling; Solid phase synthesis; Combinatorial chemistry