Homogeneous Catalysis

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A General and Selective Copper-Catalyzed Cross-Coupling of Tertiary Grignard Reagents with Azacyclic Electrophiles**

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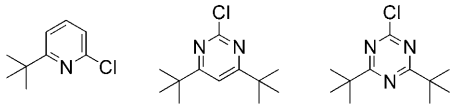
Catalytic cross-coupling reactions continue to revolutionize the way of constructing C–C bonds, particularly for olefinic, aromatic, and heteroaromatic compounds.[1] The cross-coupling reactions of C(sp^3)-centered substrates bearing β-hydrogen atoms remains challenging because of the competing β-hydride elimination and isomerization[2] of the catalyst-bound alkyl groups.[3] The catalytic cross-coupling of sterically hindered tertiary alkyl nucleophiles is considered to be particularly difficult,[4] and such reactions have not been investigated systematically.[5–9] We present herein a general and selective copper-catalyzed cross-coupling of tertiary Grignard reagents with chloro-azacyclic electrophiles which gives access to a range of heterocyclic building blocks for use in supramolecular chemistry,[10] molecular opto-electronics,[11] and pharmaceutical chemistry,[8e,12,13] and in the preparation of valuable bifunctional ligands for transition-metal catalysis.[14]

In our work on bifunctional catalysis with bulky aza-aryl phosphane ligands,[15] we needed heterocyclic building blocks (**1a–c**) containing tertiary alkyl groups and electrophilic sites



1a **1b** **1c**

for additional synthetic elaboration. These heterocycles tend to be synthesized in lengthy and, at times, low-yielding condensation routes.[16,17] Alternative syntheses involving metal-catalyzed tertiary alkylation address the above-mentioned problems and solve the issue of regioselective mono- versus di- or trisubstitution in doubly or triply chlorinated substrates.[18] Fürstner and co-workers have addressed the latter problem for the iron-catalyzed alkylations of dichloroazacycles[19] with Grignard reagents, but an extension of their protocol to tertiary alkyl nucleophiles was unsuccessful.[20]

When we combined *t*BuMgCl with either 2,6-dichloropyridine (**2a**) or cyanuric chloride (**2c**) at ambient temperature, in the absence of a catalyst, substitution products were not formed.[21] However, the addition of a catalytic amount (3–5 mol%) of copper(I) iodide to the same reactant combination led to a selective catalytic cross-coupling; namely, **2a** was converted in high yield into **1a** with only a trace (< 0.5%) of the accompanying disubstituted product (Table 1). A catalytic quantity of copper is all that is needed to achieve the highly selective monosubstitution of dichloropyridine (**2a**).[22] This simple, yet highly efficient protocol was additionally explored for a range of chloroazacycles (Table 1).[23] Selective monosubstitution was also observed with quinazolines **2d** and **2e**, and quinoxaline **2f** (Table 1, entries 3–5). Trichloroazacycles such as pyrimidine **2b** and cyanuric chloride (**2c**) were readily converted into disubstituted products (Table 1, entries 7, 8, and 11). Limiting the amount of the Grignard reagent and lowering of the reaction temperature led to selective monoalkylations (Table 1, entries 6, 9, and 10). The latter conditions may be compared to those of a noncatalyzed alkylation (**2c**→**3c**: 112°C, 3.5 h, 24% yield)[24] to illustrate the impressive catalytic acceleration by copper(I). Trisubstitution was achieved in the case of cyanuric chloride (**2c**) by performing consecutive alkylations in one pot (Table 1, entry 12). The results in Table 1 imply that the catalytic substitution is sensitive to electronic effects, because the ease and rate of alkylation increase with each additional chlorine or ring-nitrogen atom in the substrate. The selectivity profile includes a peculiar specificity for tertiary Grignard reagents; analogous reactions of **2a** with either secondary alkyl (isopropyl, cyclohexyl) or aryl nucleophiles gave mixtures containing monosubstituted, disubstituted, dehalogenated, or reductively coupled products, in addition to unreacted starting material.

The reaction was also extended to higher tertiary Grignard reagents (Table 2). Dimethylalkyl (Table 2, entries 1–7), cycloaliphatic (Table 2, entry 8), and cage-type Grignard reagents (Table 2, entries 12 and 13) underwent the cross-coupling reaction. Limitations became apparent only for combinations of the most hindered Grignard reagent reacting with the least active substrate (**2a**; Table 2, entry 9). The products in Table 2 are new compounds which would be difficult to obtain by other methods.[25] The immediate practical value of the new cross-coupling reaction is exemplified by the straightforward syntheses of compounds that have been previously obtained by involved procedures (Scheme 1).

Phosphane **14**[17] having a shielded pyridine unit is a powerful ligand for bifunctional catalysis,[14] including the ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes.[15,26] The previous synthesis (6 steps, 3.3% overall yield)[17] is now replaced by the two-step protocol shown in Scheme 1 (62% overall yield). The *tert*-amylpyridylphos-

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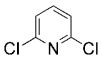
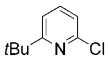
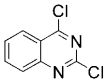
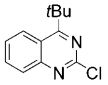
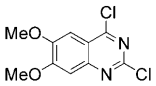
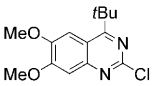
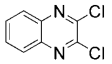
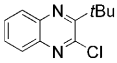
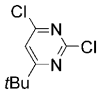
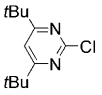
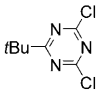
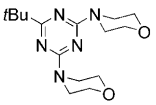
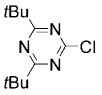
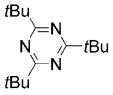
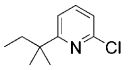
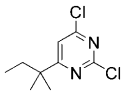
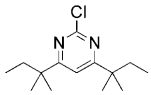
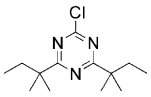
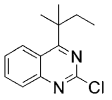
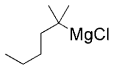
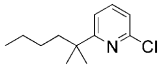
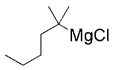
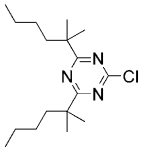
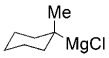
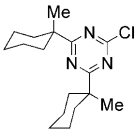
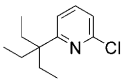
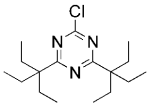
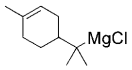
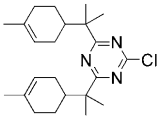
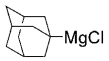
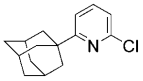
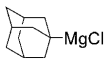
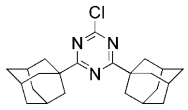
Table 1: Copper-catalyzed cross-coupling of chloroazacycles with *tert*-butylmagnesium chloride.

Entry	Substrate	*t*BuMgCl [equiv]	CuI [mol%]	*T* [°C][a]	*t* [h]	Product	Yield [%]
							
1	**2a**	1.5	3	A	< 20	**1a**	84
2	**2a**	1.5	5	A	6	**1a**	85
							
3	**2d**	1.05	5	B	0.3	**1d**	92
							
4	**2e**	2.5	5	B	0.25	**1e**	63
							
5	**2f**	1.5	5	D	0.3	**1f**	67
							
6	**2b**	1.0	5	B	1.5	**3b**	98
							
7	**2b**	2.5	5	B	3	**1b**	71
8	**2b**	2.5	10	C	2	**1b**	83
							
9	**2c**	1.05	5	C	0.5	**3c**	64[b]
							
10	**2c**	1.05	5	C	0.5	**4c**	90
							
11	**2c**	2.4	3.5	B	1	**1c**	90
							
12	**2c**	1. 2.5	5	A	1	**5c**	51
		2. 2.0	3	A	48		

[a] Temperature protocol A: from 0°C→RT; B: at 0°C; C: from −10→0°C; D: at −10°C. [b] Losses because of partial hydrolysis.

phane (**15**; tampyphos)[27] is obtained analogously from **6a**; it is slightly superior to **14** as a ligand in the ruthenium catalysis.[15,28] As a second example, the reductive homocoupling of **1a** provides, for the first time, a selective and high-yielding synthesis of **16**, which is of interest as a bulky 2,2′-bipyridine ligand for transition metals. Thirdly, a series of 2-aryl-6-*tert*-butylpyridines including **17**, which was needed to study immunosuppressive reagents, can be made by a multistep synthesis from pinacolone;[12] however, **17** can now be made by a straightforward Kumada arylation[29] of **1a**. The copper catalyst for the tertiary alkylation of dichloroazacylces is compatible with a nickel-catalyzed cross-coupling; there-

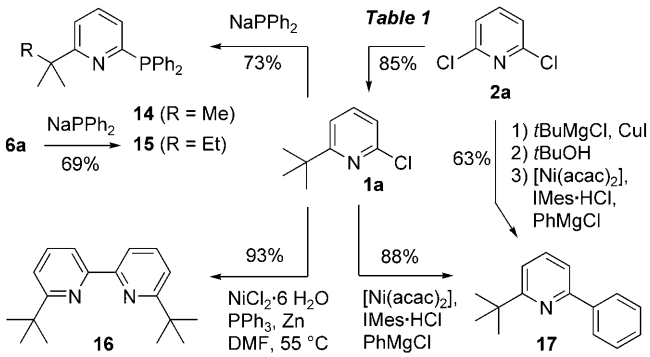
Table 2: Catalytic cross-coupling of chloroazacycles with higher tertiary Grignard reagents.

Entry	Substrate	Reagent	Equiv	CuI [mol%]	*T* [°C][a]	*t* [h]	Product		Yield [%]
1	**2a**		2.0	5	A	< 40		**6a**	74
2	**2b**		1.0	3	B	0.3		**7b**	95
3	**2b**		2.5	10	B	2		**6b**	64[b]
4	**2c**		2.1	5	D	1		**6c**	90
5	**2d**		1.05	5	D	0.3		**6d**	88
6	**2a**		1.5	5	A	16		**8a**	81
7	**2c**		2.2	5	A	1		**9c**	93
8	**2c**		2.4	5	A	2.5		**10c**	88
9	**2a**		2.4	10	A	104		**11a**	15
10	**2c**		2.2	5	A	2		**11c**	80
11	**2c**		2.2	5	A	6		**12c**	83
12	**2a**		1.6	10	A	24		**13a**	62
13	**2c**		2.5	5	A	4		**13c**	67

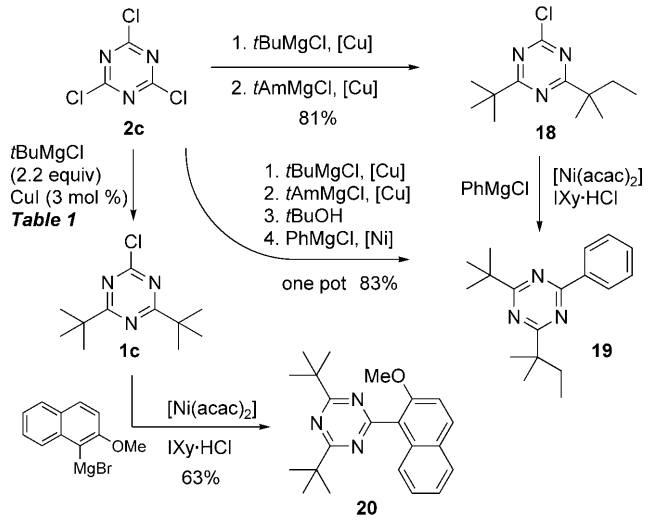
[a] Temperature protocols: A: from 0°C→RT; B: at 0°C; D: at −10°C. [b] As a side product, 4-*tert*-amyl-2-chloro-1,3-diazine was obtained in 33% yield.

fore a one-pot two-step catalytic synthesis of **17** directly from **2a** can be realized (Scheme 1).

To illustrate the synthetic flexibility that can be achieved in building up molecular structures by using the new tertiary alkylation reaction, a set of consecutive catalytic cross-coupling reactions with triazine building blocks is presented in Scheme 2. The stepwise alkylation of cyanuric chloride (**2c**) with *t*BuMgCl and *t*AmMgCl gives mixed chlorotriazine **18**, which is readily arylated[29] to the fully carbon-substituted triazine **19**. Notably, a stepwise one-pot triple functionalization of cyanuric chloride (**2c**) is achieved by consecutive additions of the required Grignard reagents and catalysts (**2c**→**19**, Scheme 2). Steric hindrance in these bulky heterocyclic building blocks is not problematic, as evidenced by the successful Kumada coupling[29] of **1c**, even with a bis(*ortho*-substituted) aryl donor (**1c**→**20**, Scheme 2).



Scheme 1. Efficient entries into the synthesis of ligands for transition metals or heterocyclic building blocks by a copper-catalyzed tertiary butylation of 2,6-dichloropyridine (**2a**). IMes·HCl = 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride.



Scheme 2. Elaboration of triazine building blocks from **2c**. IXy·HCl = 1,3-bis(2,6-dimethylphenyl)imidazolium chloride.[30]

In conclusion, we have presented a general cross-coupling reaction for tertiary Grignard compounds with heteroaryl electrophiles. This copper-catalyzed reaction selectively converts dichloroazacycles into monosubstituted chloroazacycles and trichloroazacycles into either monosubstituted dichloroazacycles or disubstituted monochloroazacycles, all of which are difficult to access otherwise. The protocol is useful for the synthesis of heterocyclic building blocks with applications in materials science, supramolecular chemistry, pharmaceutical chemistry, and coordination chemistry or catalysis.[28]

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Keywords: copper · cross-coupling · heterocycles · magnesium

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