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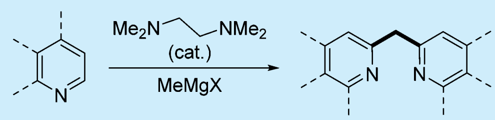
Organocatalytic Synthesis of Methylene-Bridged *N*-Heterobiaryls

David E. Stephens, Vu T. Nguyen, Bhuwan Chhetri, Emily R. Clark, Hadi D. Arman, and Oleg V. Larionov*

Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States

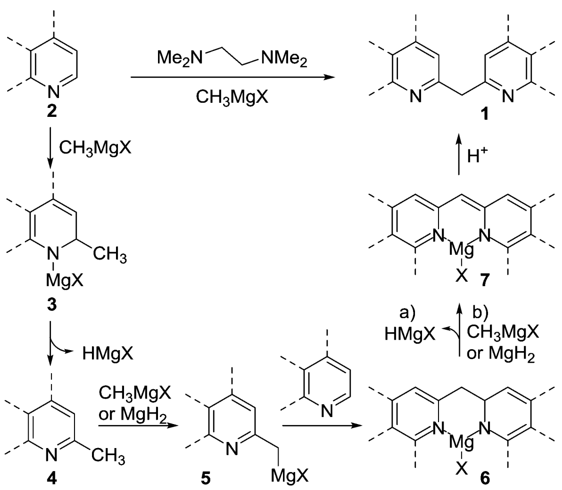
Supporting Information

ABSTRACT: A one-step synthesis of 1,1′- and 2,2′-methylene-bridged *N*-heterobiaryls directly from the corresponding *N*-heterocycles in a reaction with methylmagnesium chloride in the presence of catalytic amounts of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine under thermal and microwave conditions is reported. The split-and-merge methylenation of 2,2′-*N*-heterobiaryls and the direct *ortho*-alkylation of quinoline and isoquinoline with Grignard reagents have also been developed. Mechanistic studies identified several intermediates and provided insight into the formation and roles of magnesium hydride species in the process.



o-Methylene-bridged *N*-heterobiaryls **1** are an important class of nitrogenous heterocycles with applications in drug discovery,[1] catalyst and ligand design,[2] and materials science.[3] Previously, they were synthesized in several steps[2b] or at very high temperatures.[4] We hypothesized that **1** could be accessed directly from the corresponding *N*-heterocycles **2** by a reaction with methylmagnesium halide (Scheme 1). In this case, addition of the Grignard reagent to **2** would produce intermediate **3** that could undergo elimination of HMgX. Disproportionation of MgHX produces magnesium hydride and magnesium halide, as previously observed in Singaram pinacol boronate ester synthesis.[5,6] Deprotonation of 2-methylazine **4** would produce anionic species **5** that can add to **2** to give chelate **6**. Subsequent elimination of HMgX and deprotonation of the methylene group would furnish intermediate **7** that would produce *o*-methylene-bridged *N*-heterobiaryl **1** upon aqueous workup.

Scheme 1. Direct Synthesis of *o*-Methylene-Bridged *N*-Heterobiaryls from *N*-Heterocycles

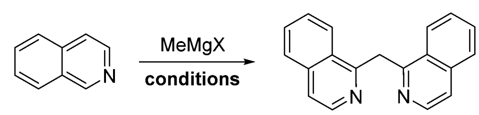


We report herein that the scalable synthesis of *o*-methylene-bridged *N*-heterobiaryls **1** can be accomplished directly from the corresponding *N*-heterocycles in the presence of catalytic amounts of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine).

Initial experiments showed that di(isoquinolin-1-yl)methane (**9**) is produced in 7% yield on treatment of isoquinoline (**8**) with MeMgCl in hexane at 120 °C (Table 1, entry 1). Addition of TMEDA led to a significant improvement of the yield (entries 2 and 3).

The optimal temperature range was 120−140 °C, and hexane and toluene were both suitable solvents. Other amines were inferior to TMEDA (entries 4−6), and the starting material

Table 1. Reaction Conditions for the Synthesis of *o*-Methylene-Bridged *N*-Heterobiaryls[a]



8 9

entry	amine (equiv)	X	solvent	time (h)	temp (°C)	yield (%)
1		Cl	hexane	2	120	7
2	TMEDA (1.3)	Cl	toluene	2	120	93
3	TMEDA (1.3)	Cl	hexane	2	120	78
4	DABCO (1.3)	Cl	hexane	2	120	7
5	PMDTA (1.3)	Cl	hexane	2	120	15
6	DMEDA (1.3)	Cl	hexane	2	120	0
7	TMEDA (0.2)	Cl	toluene	14	140	95
8[b]	TMEDA (0.1)	Br	toluene	14	140	97
9[b]	TMEDA (0.1)	I	toluene	14	140	65

[a]Isoquinoline (2 mmol), MeMgX (3 equiv), solvent (2 mL). 1,4-Dimethoxybenzene was used as an internal standard added prior to workup. [b]1 mL of toluene was used. PMDTA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine. DMEDA = *N*,*N*′-dimethylethylenediamine.

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remained largely unconsumed. Further experiments showed that the reaction can be carried out efficiently with catalytic amounts of TMEDA (entries 7 and 8). Both methylmagnesium chloride and bromide worked well, while a lower yield was observed for MeMgI (entries 7–9).

The reaction tolerates a number of functional groups (Figure 1). Quinolines and isoquinolines with substituents in the 3, 4, 5,

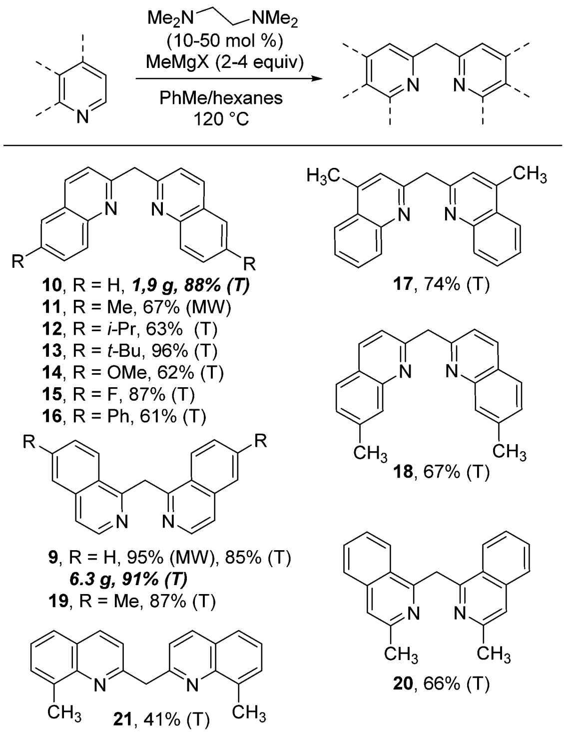


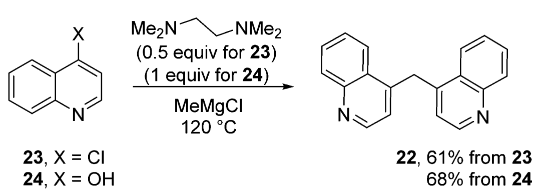
Figure 1. Organocatalytic synthesis of *o*-methylene-bridged *N*-heterobiaryls.

6, and 7 positions have produced the corresponding *o*-methylene-bridged biquinolines and biisoquinolines (**8**, **10**–**21**) in good to excellent yields. The reaction was also successfully carried out under microwave irradiation. Further, products **9** and **10** were synthesized on a preparative scale (6.3 and 1.9 g, respectively).

Quinolines reacted regioselectively at the C2 position, while isoquinolines produced the 1,1′-methylene-bridged products. C2-methylene-bridged bipyridines were not observed when pyridines were subjected to the standard reaction conditions.

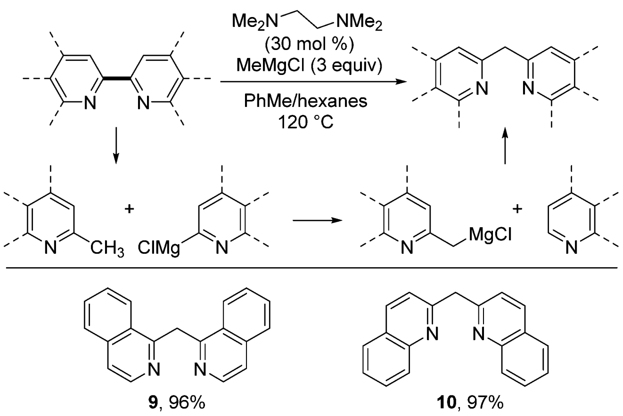
4,4′-Methylene-bridged biquinoline **22** was readily obtained by a reaction of 4-chloroquinoline **23** with MeMgCl in the presence of TMEDA (Scheme 2). 4-Hydroxyquinolne (**24**) also produced 4,4′-methylene-bridged biquinoline **22**, indicating that 4-hydroxy group can be readily displaced by a Grignard reagent under these conditions.

Scheme 2. Synthesis of 4,4′-Methylene-Bridged *N*-Heterobiaryls



Interestingly, 1,1′-biisoquinoline and 2,2′-biquinoline underwent a C−C bond cleavage with subsequent formation of the methylene-bridged products **9** and **10** in excellent yields, indicating that an unusual and facile *C*-nucleophile/*C*-nucleofuge displacement takes place under the reaction conditions (Scheme 3). Since substituted 1,1′-biisoquinolines

Scheme 3. Split and Merge Synthesis of *o*-Methylene-Bridged *N*-Heterobiaryls from 2,2′-Biquinoline and 1,1′-Biisoquinoline



and 2,2′-biquinolines can be prepared in a scalable manner from the corresponding *N*-oxides,[7] this route offers additional flexibility in the synthesis of *o*-methylene-bridged *N*-heterobiaryls.

We have further investigated the reactions of quinoline and isoquinoline with other alkylmagnesium halides (Figure 2). The

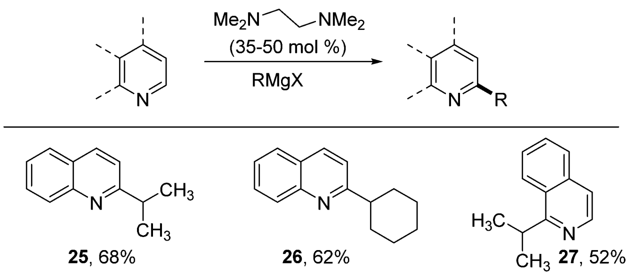


Figure 2. Synthesis of 2-alkylquinolines and 2-alkylisoquinolines.

reactions did not produce *o*-methylene-bridged *N*-heterobiaryls but instead afforded the corresponding 2-alkylquinolines (**25** and **26**) and 1-isopropylisoquinoline (**27**). These results are in agreement with the observation of TMEDA-catalyzed arylation of azines with arylmagnesium bromides reported by Da et al.[8] No functionalization of the distal positions[9] was observed for quinolines and isoquinoline. This direct alkylation reaction is complementary to the deoxygenative *ortho*-alkylation of heterocyclic *N*-oxides.[10]

Several experiments were carried out to clarify the mechanism of the reaction. First, monitoring of the reaction of isoquinoline with methylmagnesium chloride in the presence of TMEDA in C_6D_6 at 50 °C by means of ^{1}H NMR spectroscopy identified several intermediates along the reaction pathway (Scheme 4). Formation of the Grignard addition product **28**, as well as 1-methylisoquinoline (**29**) that arises from the loss of HMgX, was observed. Further, magnesiated di(isoquinolin-1-yl)methane intermediate **30** was also detected.

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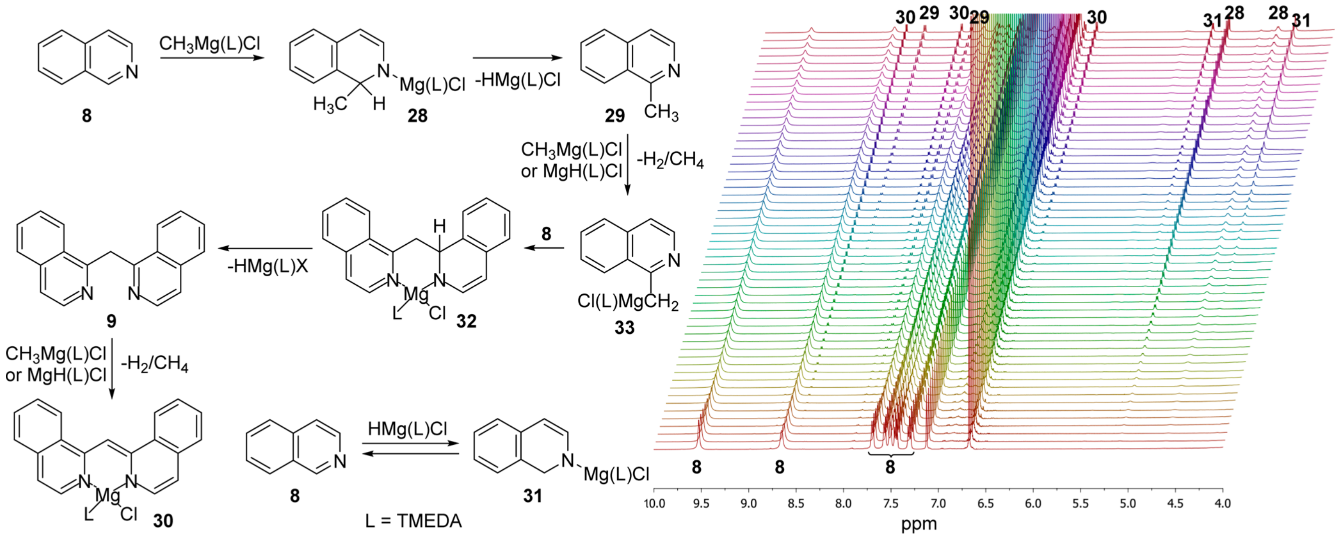
Scheme 4. Intermediates in the Reaction of Methylmagnesium Chloride with Isoquinoline



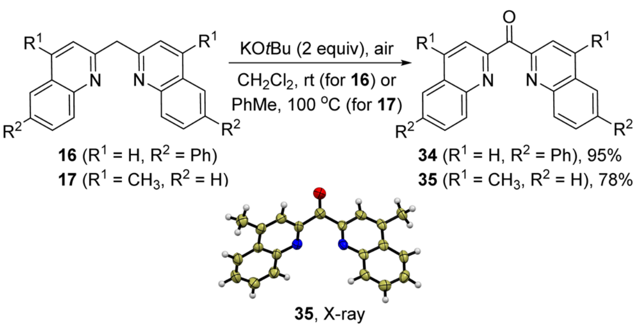
Interestingly, formation of 1,2-dihydroisoquinoline intermediate **31** was also observed. Addition of magnesium hydride species to pyridines is a reversible process.[11] Indeed, when isoquinoline-1-d_1 was heated with 25 mol % MgH_2[12] in the presence of TMEDA (1 equiv) in toluene-d_8 for 2 h at 110 °C, 20% H/D exchange (40% after 21 h) took place in the C1 position of isoquinoline, indicating that magnesium hydride addition to isoquinoline is reversible under the reaction conditions. Intermediate **31** may serve as a pool of soluble magnesium hydride species in solution. It is also possible that a hydride transfer takes place directly to isoquinoline from 1,2-dihydroisoquinoline intermediates **28** and **32**,[13] facilitating their aromatization. In order to further investigate the formation and roles of magnesium hydride species in the methylenation process, the amount of hydrogen produced in the reaction of quinoline with methylmagnesium chloride in the presence of TMEDA in hexane at 120 °C was determined by means of gas chromatography.

Interestingly, hydrogen was formed even before the reaction mixture was quenched with methanol (0.45 mmol H_2 per 1 mmol of quinoline), indicating that magnesium hydride participates in the deprotonation of intermediates **9** and **29** en route to magnesiated species **30** and **33**. Addition of methanol after the reaction led to generation of 0.7 mmol of hydrogen per 1 mmol of quinoline, in agreement with the observed 73% conversion of quinoline.

o-Methylene-bridged *N*-heterobiaryls **1** can be readily oxidized to the corresponding ketones that are useful bidentate chelators.[14] For example, diquinolinylmethanes **16** and **17** were oxidized by air in the presence of potassium *tert*-butoxide to give ketones **34** and **35** in 95% and 78% yields, respectively (Scheme 5).

In conclusion, a simple, one-step synthesis of *o*-methylene-bridged biquinolines and biisoquinolines has been developed. The reaction is catalyzed by an organic base (TMEDA). Furthermore, the efficient split and merge methylenation of biquinolines and biisoquinolines by methylmagnesium chloride in the presence of TMEDA as a catalyst has also been described. *ortho*-Alkylation of quinoline and isoquinoline has been observed with other alkylmagnesium reagents. Mechanistic studies point to a reversible elimination of magnesium hydride species en route to *o*-methylene-bridged *N*-heterobiaryls. The methylene bridge in the products of methylenation can be readily oxidized by air in the presence of potassium *tert*-butoxide.

Scheme 5. Oxidation of the Methylene Group in Diquinolinylmethanes 16 and 17



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02719.

Experimental and spectral details for all new compounds and all reactions (PDF)

X-ray crystallographic data for compound **35** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: oleg.larionov@utsa.edu.

Notes

The authors declare no competing financial interest.

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