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Regioselective lithium–halogen exchange and palladium-catalyzed cross-coupling reactions of 2,4-dihaloquinolines

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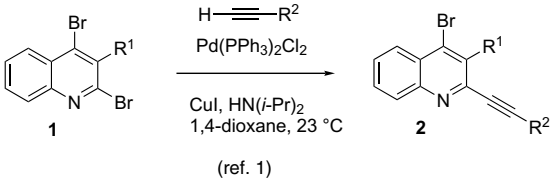
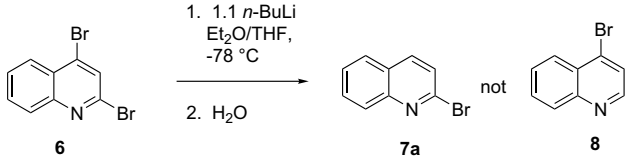
Abstract—Lithium–halogen exchange of 2,4-dibromoquinolines proceeds regioselectively at C-4 and affords 4-substituted quinolines on quenching with electrophiles. Palladium-catalyzed cross-coupling reactions of 2-bromo-4-iodoquinoline provide 4-substituted 2-bromoquinoline derivatives.

We recently published a report on the regioselective Sonogashira coupling of 2,4-dibromoquinolines.[1] Using HMBC correlations and other NMR data, we proved that this reaction was general and selective for the C-2 position of the quinolines (Scheme 1).

It has been suggested that selectivity of this type is a result of a mechanism in which the lone pair of the nitrogen coordinates to the metal and directs substitution to the C-2 position.[2] It is known that C-2 selectivity is also general for analogous 2,4-dibromo-[3] and 2,5-dibromopyridines.[4] Conversely, it has been demonstrated that 2,4-dibromopyridines will undergo a regioselective lithium–halogen exchange reaction[5] at C-4 to afford 4-substituted 2-bromopyridines on addition of electrophiles.[6]



Scheme 1.



Scheme 2.

Owing to the fact that not all pyridine chemistry is directly applicable to quinolines,[7] an investigation of the reactivity of 2,4-dibromoquinolines toward lithium–halogen exchange was undertaken. Treatment of 2,4-dibromoquinoline with 1.1 equiv of *n*-BuLi (Et_2O/THF, −78 °C) provided a lithioquinoline which was quenched with water (Scheme 2).

The resulting product was determined to be 2-bromoquinoline by comparison[8] with authentic samples of **7a** and **8**.[9] To determine if this reaction was general for other electrophiles, a study was carried out and the results are shown in Table 1. The anticipated products **7b–f** were obtained in good to high yields.

In contrast to the reactivity of 2,4-dibromoquinoline, when 2-bromo-4-iodoquinoline (**7b**) was subjected to Sonogashira coupling conditions, the product was determined to be the 4-substituted quinoline **9** (Scheme 3).

The product **9** was afforded in 90% yield after 2 h at room temperature. To determine if 2-bromo-4-iodoquinoline could be selectively substituted at C-4 using

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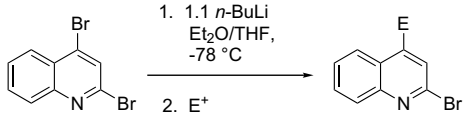
Table 1. Examples of C-4 substitution of **6**[a]

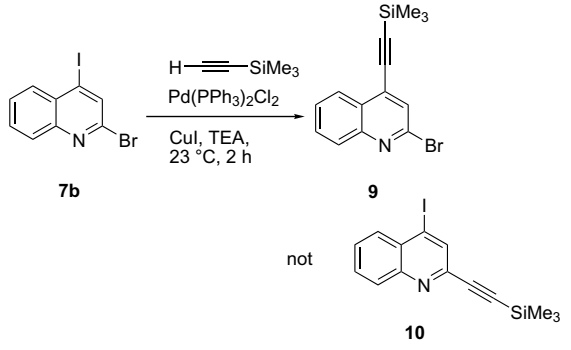


6

7a, E = H, **7b**, E = I, **7c**, E = Me
7d, E = $SiMe_3$, **7e**, E = CHO
7f, E = CH(OH)Ph

Entry	E^+	Product	Yield[b] (%)
1	H_2O	**7a**	76
2	I_2	**7b**	87
3	MeI	**7c**	85[c]
4	TMSCl	**7d**	70
5	DMF	**7e**	74
6	PhCHO	**7f**	82

[a] The reactions were performed on a 0.1–1.0 mmol scale.
[b] All yields are for isolated products after chromatography.
[c] Purity determined to be 94% by ^{1}H NMR analysis.[10]



7b **9** **10**

Scheme 3.

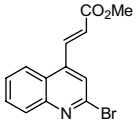
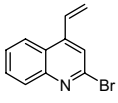
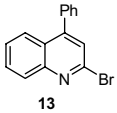
other palladium-catalyzed cross-coupling reactions, a study was carried out and the results are shown in Table 2.

To establish if additional functionality can be present at C-3 during the regioselective lithium–halogen exchange, the known 2,4-dibromo-3-quinolinecarboxaldehyde (**14**)[1] was protected in situ as an α-amino alkoxide[13] and treated with *n*-BuLi. Addition of iodine to the resulting dianion **15** provided quinolinecarboxaldehyde **17** in 90% yield. Similarly, the more reactive dianion **16** was treated with MeSSMe to give quinoline derivative **18**. In addition, the dianion **20** was prepared from alcohol **19**[1] and treated with iodine to give quinoline **21** in high yield (Scheme 4).

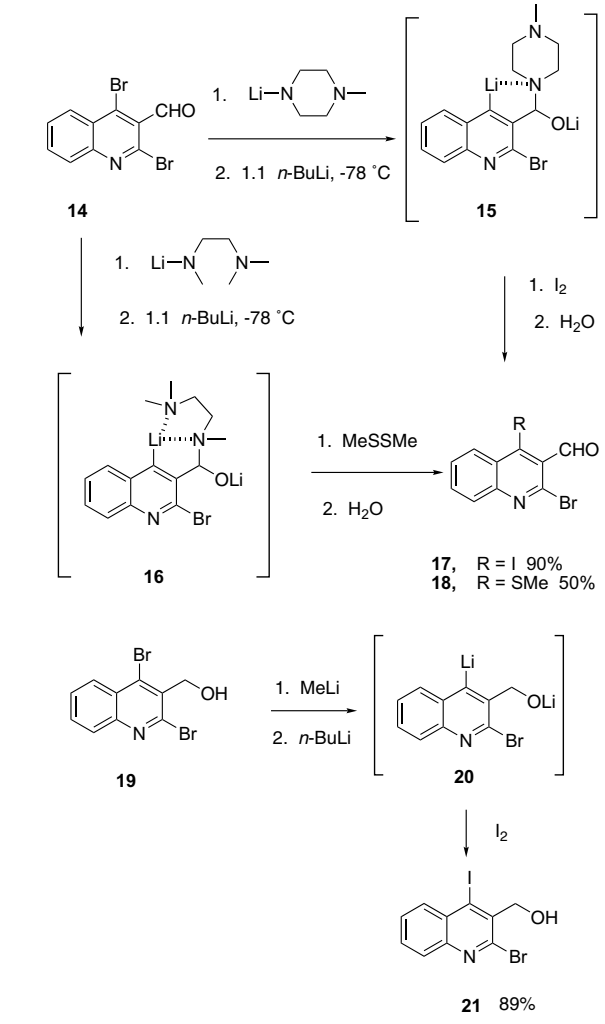
The Sonogashira reaction on quinolines **17** and **21** was briefly examined. Trimethylsilylacetylene and **17** gave a mixture of 4- and 2,4-disubstituted products (**22** and **23**) along with recovered starting material. The analogous reaction with quinoline **21** afforded an inseparable mixture of 2- and 4-substituted isomers **24** and **25** (Scheme 5).

In summary, the lithium–halogen exchange reaction of 2,4-dibromoquinoline provides a method for synthesizing 4-substituted 2-bromoquinolines with identical regioselectivity as found in the pyridine series. This selectivity is understood to arise from the stability of the lithioquinoline intermediate, which is most stable when the aryl–lithium bond is furthest from the nitrogen lone pair.[14] In this report, we also presented a new method for regioselective palladium-catalyzed cross-couplings of 2,4-dihaloquinolines at the C-4 position. This selectivity is complementary to our previously published work, in which substitution was selective for the C-2 position.[1] With 2-bromo-4-iodoquinoline, the Suzuki, Stille, Sonogashira, and Heck reactions all proceeded with excellent C-4 regioselectivity and is a result of the greater reactivity of the aryl–iodide bond toward oxidative addition with palladium relative to the aryl–bromide bond.[15] The presence of a formyl or hydroxymethyl group at C-3 lowers the regioselectivity of the Sonogashira cross-coupling reaction.

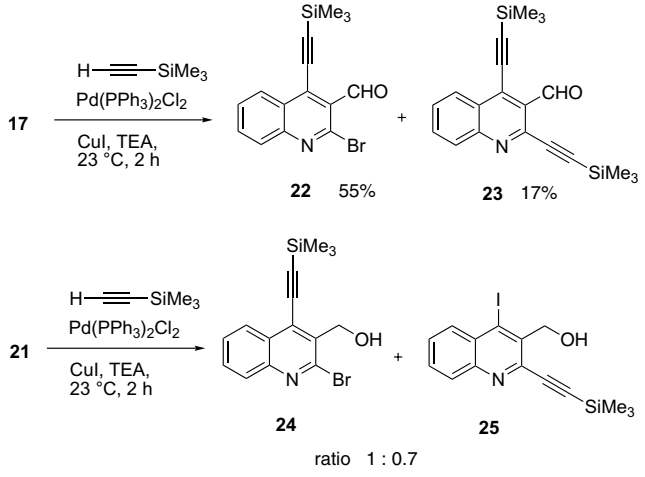
Table 2. Various palladium-catalyzed cross-coupling reactions of **7b**

Entry	Conditions	Coupling partner	Product	Yield[a] (%)
1 (Heck)	$Pd(PPh_3)_2OAc_2$, KOAc, CH_3CN, 80 °C, 24 h	CH_2=CH–CO_2Me	 **11**	33[b]
2 (Stille)	$Pd(PPh_3)_2Cl_2$, DMF, 80 °C, 18 h[c]	CH_2=CH–$SnBu_3$	 **12**	63[d]
3 (Suzuki)	$Pd(PPh_3)_2Cl_2$, 2.0 M K_2CO_3, THF, 20 h, Δ[e]	Ph–$B(OH)_2$	 **13**	55

[a] Reported yields are for isolated products and are unoptimized.
[b] Compound **7b** was recovered in 30% yield.
[c] Ref. 11.
[d] Compound **7b** was recovered in 12% yield.
[e] Ref. 12.



Scheme 4.



Scheme 5.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.137. Experimental for the preparation of **7b**, **9**, and **17**, characterization data for compounds **7a–f**, **9**, **11–13**, **17–18**, and **21–23**.

References and notes

1. Nolan, J. M.; Comins, D. L. *J. Org. Chem.* **2003**, *68*, 3736.
2. Shiota, T.; Yamamori, T. *J. Org. Chem.* **1999**, *64*, 453, and references therein.
3. Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386.
4. Chambers, R. D.; Hall, C. W.; Hutchinson, J.; Millar, R. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1705.
5. Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.
6. Bouillon, A.; Lancelot, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.
7. Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed; A.W. Longman: England, 1977, Chapter 5.
8. The product's structure was determined using mp, ^{1}H- and ^{13}C NMR.
9. (a) Both 2-bromoquinoline and 4-bromoquinoline were synthesized from the corresponding hydroxyquinoline and their respective data matched the literature values: Sugimoto, O.; Mori, M.; Moriya, K.; Tanji, K. *Helv. Chim. Acta* **2001**, *84*, 1112; (b) Ono, I.; Hata, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2891.
10. The impurity was determined to be 2′-bromo-4-methyl-[2,4′]biquinolinyl by ^{1}H NMR. For entries 2–4 of Table 1 the product is reactive with the lithioquinoline intermediate, and it is favorable to use inverse addition in those cases.
11. Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Baldwin, J. E., Williams, F. R. S., Williams, R. M., Eds.; Elsevier Science Ltd: Oxford, 2000, p 207.
12. Couve-Bonnaire, S.; Carpentier, J.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* **2001**, *42*, 3689.
13. Review: Comins, D. L. *Synlett* **1992**, 615–625.
14. Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059.
15. Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998, p 203.