ORGANIC LETTERS

2009
Vol. 11, No. 6
1237−1240

Intramolecular Carbolithiation Reactions for the Synthesis of 2,4-Disubstituted Tetrahydro-quinolines: Evaluation of TMEDA and (−)-Sparteine as Ligands in the Stereoselectivity†

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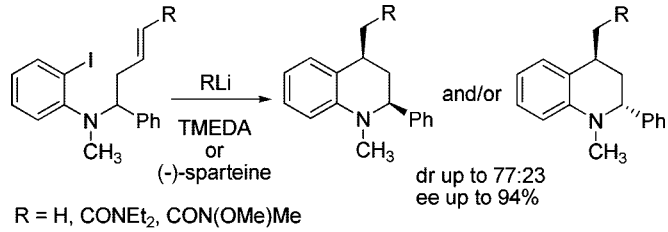
Received January 13, 2009

ABSTRACT



The preparation of 4-substituted 2-phenyltetrahydroquinolines from *N*-alkenylsubstituted 2-iodoanilines via intramolecular carbolithiation reactions has been investigated. The stereochemical outcome of the carbolithiation reactions depends on the nature of organolithium employed to perform the lithium-halogen exchange, the solvent, or the use of additives, for example, TMEDA or chiral bidentated ligands such as (−)-sparteine. Thus, the 2,4-disubstituted tetrahydroquinolines are obtained with moderate diastereoselectivities (up to 77:23) and with ee up to 94% when Weinreb amide derivatives are used (R = CONMe(OMe)).

The intramolecular carbolithiation[1] of alkenes and alkynes has recently emerged as an interesting approach for the synthesis of functionalized five-member carbocyclic and heterocyclic systems. The attraction of this methodology lies in the high regio- and stereoslectectivity when a carbon−carbon bond is formed and in the possibility of trapping the resulting cyclized organolithium with various electrophiles to introduce diverse functionality into the cyclized products. Although many of these carbolithiations involve alkyl or alkenyllithiums,[2] there are also some examples of cycloisomerization of alkenyl substituted aryllithiums generated by metal−halogen exchange.[3] Thus, an intramolecular carbolithiation reaction of unsaturated aryllithiums is particularly well suited for the

† Dedicated to Prof. Josep Font on the occasion of his 70th birthday.

(1) For reviews, see: (a) Marek, I. *J. Chem. Soc., Perkin 1* **1999**, 535–544. (b) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59–67. (c) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: New York, 2002; pp 282−335. (d) Normant, J. F. *Top. Organomet. Chem.* **2003**, 287–310. (e) Fañanás, F. J.; Sanz, R. In *The Chemistry of Organolithium Compounds*; Patai Series: The Chemistry of Functional Groups, Vol. 2; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2006; Chapter 4, pp 295−379.

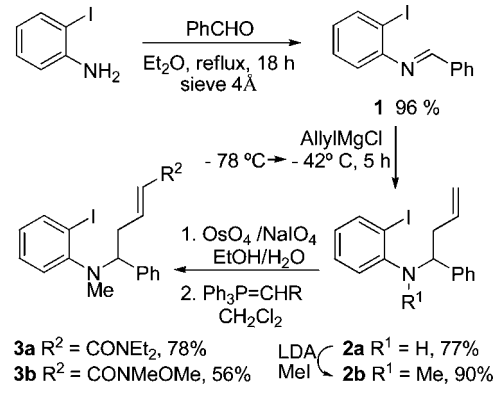
(2) For some representative examples, see: (a) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788–4796. (b) Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7023–7024. (c) Bailey, W. F.; Jiang, X.-L.; McLeod, C. E. *J. Org. Chem.* **1995**, *60*, 7791–7795. (d) Krief, A.; Kenda, B.; Remacle, B. *Tetrahedron* **1996**, *52*, 7435–7463. (e) Coldham, I.; Hufton, R; Price, K. N.; Rathmell, R. E.; Snowden, D. J.; Vennall, G. P. *Synthesis* **2001**, 1523–1531. (f) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106–12107. (g) Sanz, R.; Ignacio, J.; Rodríguez, M. A.; Fañañas, F. J.; Barluenga, J. *Chem.−Eur. J.* **2007**, *13*, 4998–5008. The procedure has also been extended to the corresponding alkyne derivatives; see, for instance: (h) Wu, G.; Cederbaum, F. E.; Negishi, E. *Tetrahedron Lett.* **1990**, *31*, 493–496.

10.1021/ol900066c CCC: $40.75
Published on Web 02/17/2009

construction of five-membered rings through a 5-*exo*-trig cyclization process, as it has been shown in the synthesis of carbocyclic[4] and heterocyclic compounds,[5] even in a diastereoselective[6] or enantioselective fashion.[7,8] However, some limitations have precluded the general applicability of this method. In fact, the above-cited examples consist of intramolecular carbolithiations to five-membered rings and it remains unclear whether cyclization to six-membered cycles would provide the same degree of stereo- and regiochemical efficiency. Only a few examples of *6-exo* cyclization process via intramolecular carbolithiations involving alkyl or alkenyllithiums have been reported.[9] Regarding aryllithiums, Pedrosa[10] et al. have described the synthesis of enantiopure 4-substituted tetrahydroisoquinolines *via* a diastereoselective *6-exo* carbolithiation of unactivated double bonds in chiral (−)-8-aminomenthol derived perhydro-1,3-benzoxazines. Recently, we have also reported[11] the synthesis of the pyrrolo[1,2-*b*]isoquinoline system through MesLi-mediated intramolecular carbolithiation reactions of *N*-(*o*-iodobenzyl)pyrroles, though in our case the alkene is required to be substituted with an electron withdrawing group.

Therefore, in connection with our work[12] on Parham-type cyclizations,[13] we decided to investigate the intramolecular carbolithiation for the synthesis of 2,4-disubstituted tetrahydroquinolines. Herein we describe the cyclization of the aryllithiums generated from *N*-alkenyl substituted *o*-iodoanilines to the tetrahydroquinoline derivatives, using alkenes

Scheme 1. Synthesis of *N*-Alkenyl Substituted *o*-Iodoanilines **2a**,**b** and **3a**,**b**



with different substitution patterns as internal electrophiles. We have also examined the effect of bidentate ligands, such as TMEDA and (−)-sparteine, in the stereoselectivity of these carbolithiation reactions.

To test the carbolithiation reactions, we first prepared the *N*-alkenyl substituted *o*-iodoanilines **2** and **3** by standard methodologies (Scheme 1). Condensation of *o*-iodoaniline and benzaldehyde, followed by addition of allylmagnesium chloride led to secondary amine **2a**, which was alkylated with LDA and MeI, thus affording amine **2b**.[14] Oxidative cleavage of the alkene double bond with OsO_4/$NaIO_4$ led to the corresponding aldehyde, whose *in situ* olefination was was achieved via Wittig reaction with the corresponding phosphorus ylides to afford *N*-alkenyl substituted *o*-iodoanilines **3a**,**b**[15] in good overall yields (Scheme 1).

We first studied the carbolithiation reactions of *o*-iodoaniline **2a** with *t*-BuLi (Table 1), starting under standard conditions (2 equiv of RLi, THF, −78 °C). However, although iodine−lithium occurred efficiently, since dehalogenated amine was always isolated (entries 1 and 2), intramolecular carbolithiation did not take place. We next tried the addition of a bidentate ligand as TMEDA, which

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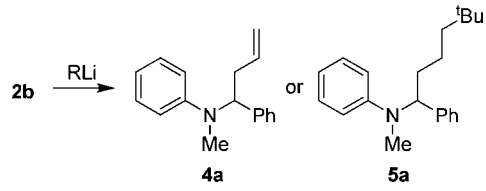
(14) All attempts to prepare **2b** by quenching the addition reaction with MeI failed.

(15) Attempts to introduce the electron withdrawing group directly on **2b** by cross metatethesis with acryl amides in the presence of 1st and 2nd generation Grubbs' catalysts failed, leading only to dimeric product derived from **2b**. Besides, addition of functionalized allyl organomagnesium reagents to imine **1** also faliled.

Table 1. Carbolithiation Reactions of *o*-Iodoaniline **2b**



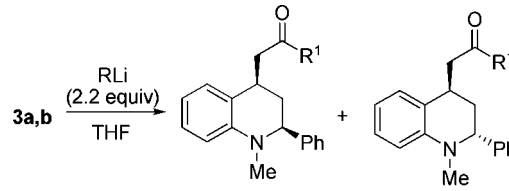
	t-BuLi (equiv)	TMEDA (equiv)	temp (°C)	time	prod	yield (%)
1	2.2[a]	–	−78	3 h	**4a**	80
2	2.2[a]	–	−78 to rt	7 h	**4a**	65
3	1.1[b]	1.1	−78 to 0	40 min	**4a**[c]	60
4	2.2[b]	2.2	−78 to 0	40 min	**5a**	60
5	2.2[b]	2.2	−78	30 min	**4a**	95
6	1.1[d]	1.1	−78 to 45	45 min	**4a**[e]	20
7	2.2[d]	2.2	−78 to 45	45 min	**5a**	80

[a] Solvent THF. [b] Solvent: *n*-pentane/Et_2O (9:1). [c] *N*-methylaniline (<5%) was isolated. [d] Solvent: *n*-heptane/*t*-Bu_2O (9:1). [e] *N*-methylaniline (20%) was also isolated.

has been shown to facilitate and accelerate the rate of carbolithiation reactions.[16] The use of equimolecular amounts of *t*-BuLi/TMEDA in a less coordinating solvent system (pentane/Et_2O 9:1) also resulted in reductive dehalogenation and deiodinated amine **4b** was isolated (entry 3) when the reaction was allowed to reach 0 °C. When 2 equiv of *t*-Buli were employed under the same conditions, addition of *t*-Buli to the unsubstituted alkene in **2b** was competitive with cyclization, isolating **5a** (Table 1, entry 4). This side reaction could be avoided quenching the reaction at −78 °C, though **4a** was again the only reaction product (entry 5). It has been shown that the rate of carbolithiation reactions can be increased performing the reactions at higher temperatures,[17] so the reaction mixtures were warmed to 45 °C, using *n*-heptane/*t*-Bu_2O (9:1) as solvent to avoid protonation of the intermediate aryllithium (entries 6 and 7), but similar results were obtained, isolating also decomposition products, as *N*-methylaniline.

Therefore, we studied the carbolithiation reactions on **3a** (Table 1, entries 1−8). Thus, the introduction of an electron withdrawing group on the alkene (R^1 = $CONEt_2$) allowed the cyclization, affording efficiently the corresponding tetrahydroquinolines **6a** and **7a** at −78 °C, although with almost no diastereoselectivity (entry 1). The addition of TMEDA did not improve the results (entry 2).[18] Different reaction conditions were tested to improve the yield and the stereoselectivity. In fact, the cyclization reaction was quite fast and was completed just in 10 min, even in the absence of TMEDA (entry 3). Lowering the temparature to −95 °C did

Table 2. Carbolithiation Reactions of *o*-Iodoanilines **3a**,**b**



	subs	RLi	additive 2.2 equiv	temp (°C)	time (min)	yield (%)	dr **6**:**7**
1	**3a**	*t*-BuLi	–	−78	50	73	58:42
2	**3a**	*t*-BuLi	TMEDA	−78	60	60[a]	55:45
3	**3a**	*t*-BuLi	–	−78	10	74	55:45
4	**3a**	*t*-BuLi	–	−95	8	81	56:44
5	**3a**	*t*-BuLi	TMEDA	−105	5	64[b]	61:39
6	**3a**	*n*-BuLi	–	−105	5	80	58:42
7	**3a**	*n*-BuLi	TMEDA	−105	5	81	77:23
8	**3a**	*n*-BuLi	TMEDA	−105	5	60[c]	71:29
9	**3b**	*t*-BuLi	–	−105	5	66	29:71
10	**3b**	*t*-BuLi	TMEDA	−105	5	–	
11	**3b**	*t*-BuLi	TMEDA	−105	60	–	
12	**3b**	*t*-BuLi	TMEDA	−95	60	–	
13	**3b**	*t*-BuLi	TMEDA	−45	120	–	
14	**3b**	*n*-BuLi	–	−105	5	68	40:60
15	**3b**	*n*-BuLi	TMEDA	−105	5	74[d]	59:41

[a] Solvent: Toluene. [b] Conversion: 93%. [c] Solvent: Et_2O. [d] Conversion: 73%.

not improve the selectivity (entry 4). The addition of TMEDA allows the reaction to be carried out at −105 °C in 5 min with an improved diastereoselectivity in favor of the *cis* product **6a** (entry 5). However, the best results were obtained using *n*-BuLi as metalating agent, yielding **6a** with a reasonable diastereoselectivity (77:23, entry 7). A change in the solvent to Et_2O resulted in lower yield and loss of diastereoselectivity (entry 8).

When the amide **3b** was used as substrate, the cyclization took place efficiently at −105 °C, even in the absence of TMEDA, although with opposite diastereoselectivity, obtaining mainly the *trans* product **7b** (entry 9). In the presence of TMEDA, the reaction did not take place under various conditions (entries 10−13). When *n*-BuLi was used an increased formation of the *cis* product **6a** was observed (entry 14), which was the major product in the presence of TMEDA (entry 15), although with almost no diastereoselectivity.

We next studied the posibility of performing the carbolithiation reactions in an enantioselective fashion in the presence of a chiral bidentate ligand such as (−)-sparteine.[19]

(16) See, for instance refs 2c,g, 5b, and 9. See also: Coldham, I.; Fernández, J C.; Price, K. N.; Snowden, D. J. *J. Org. Chem.* **2000**, *65*, 3788–3795.

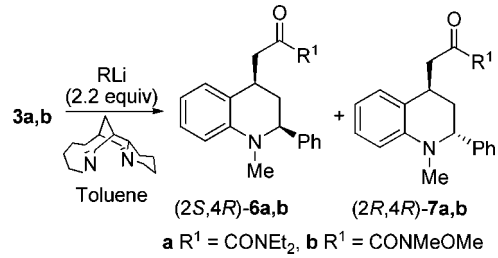
(17) Bailey, W. F.; Daskapan, T.; Rampalli, S. *J. Org. Chem.* **2003**, *68*, 1334–1338.

(18) The addition of TMEDA has been reported to influence not only the rate of the carbolithiation, but also the stereochemical outcome. See, for instance: Bailey, W. F.; Jiang, X. *Tetrahedron* **2005**, *61*, 3183–3194.

(19) For reviews of the use of sparteine as chiral ligand, see: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2283–2316. (c) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715–727. (d) Hoppe, D.; Christoph, G. In *The Chemistry of Organolithiums Compunds*; Rappoport, Z., Marek, I., Eds.; John Wiley and Sons: New York, 2004; Chapter 17, p 1055.

Thus, **3a**,**b** were added over a solution of the alkyllithium (*t*-BuLi or *n*-BuLi) and (−)-sparteine, using toluene as solvent to allow the coordination of the organolithium with the amine. As can be seen in Table 3, the stereochemical outcome was opposite to that observed with TMEDA, affording the *trans* tetrahydroquinolines **7a**,**b** as the major diastereomer. A similar reversal of the stereochemical outcome when (−)-sparteine is used instead of TMEDA has been observed in alkylation reactions, [20] although the change in the solvent from THF, that may bind to the lithium cation, to toluene may also play a role.[21] First, **3a** was treated with *t*-BuLi/(−)-sparteine under the same conditions used with TMEDA (Table 3, entry 1), but the mixture of tetrahydroquinolines **7a** and **6a** was obtained with poor diastereoselectivity and each of the diastereomers with low enantiomeric excess.[22] Several attempts were made to improve both the diastereo and the enantioselectivity, but the use of *n*-BuLi at lower temperature, reduced reaction time, or inverse addition conditions slightly improved the distereoselectivity, but not significantly the ee (entries 2−5). However, we were pleased to find that when the Weinreb amide **3b** was used as substrate, the cyclization proceeded with reasonable diastereoselectivty (entry 6) and, when *n*-BuLi is used (entry 7), with excellent ee for each of the isolated diastereomers (**6**, 92% ee and **7**, 94% ee).[23] Thus, this result indicates that in the presence of (−)-sparteine, one of the enantiomers would react more rapidly leading to the mayor stereoisomer. In summary, it has been shown that the intramolecular carbolithiation of *o*-iodoanilines affords 2-phenyltetrahydroquinolines diastereoselectively. The use of TMEDA as additive not only increases the rate of the cyclization but also favors the formation of the *cis* adducts **6**. Besides, the use of (−)-sparteine allows the enantioselective synthesis of tetrahydroquinolies. The use of the Weinreb amide derivative **3b** and *n*-BuLi as base turned out to be crucial to obtain tetrahydroquinolines **6** and **7** in high ee and dr.

Table 3. Carbolithiation Reactions of *o*-Iodoanilines **3a**,**b** in the Presence of (−)-Sparteine



entry	subs	RLi	conditions[a]	yield (%)	dr **6**/**7**	ee (%) **6**/**7**
1	**3a**	*t*-BuLi	−78, 60	91	42:58	17/5
2	**3a**	*n*-BuLi	−95, 40	59	38:62	5/13
3	**3a**	*n*-BuLi	−95, 5	63	27:73	17/33
4	**3a**	*n*-BuLi[b]	−95, 5	33	40:60	5/10
5	**3a**	*n*-BuLi[b]	−95, 5	53	42:58	7/15
6	**3b**	*t*-BuLi	−95, 10	31	30:70	8/2
7	**3b**	*n*-BuLi	−95, 10	48	33:67	92/94

[a] Conditions: temperature (°C), time (min). [b] *n*-BuLi was added over a solution of **3a**,**b** and (−)-sparteine.

Acknowledgment. Financial support from MEC (CTQ2006-01903), Gobierno Vasco (GIC07/92-IT-227-07) and UPV/EHU is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data of compounds **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900066C

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(22) The enantiomeric excess for each diastereomer was determined by comparison with the racemic mixture in all cases by CSP HPLC (Chirlacel OJ, 2% hexane/*i*-propanol). See Supporting Information.

(23) The absolute configuration of each diastereomer was assigned by comparison with the results obtained performing the carbolithiation reaction with a substrate that incorporates a (*R*)-(−)-4-phenyl-2-oxazolidinone as chiral auxiliary. See Supporting Information.