Communication

A Method for Highly Enantioselective Ligation of Two Chiral C(sp) Stereocenters

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A Method for Highly Enantioselective Ligation of Two Chiral C(sp³) Stereocenters

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Supporting Information Placeholder

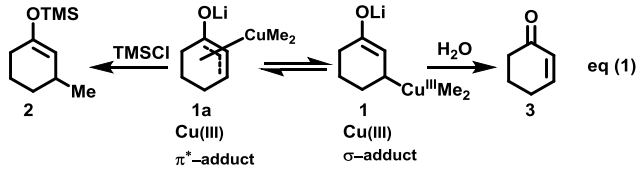
ABSTRACT: A method is described for the joining of two *α*–lithiated C(sp³)-stereocenters efficiently and with retention of configuration. The key step involves the effective removal of two electrons from a chiral organocuprate R_2CuLi, by *i*-propyl 2,4-dinitrobenzoate to form a Cu(III) complex which undergoes at –90 °C accelerated reductive elimination enantioselectively and exclusively without the formation of free radicals.

The enantioselective joining of two chiral C(sp³) stereocenters to form an enantiomerically pure product with retention of configuration at *each* chiral center has been a formidable challenge for synthetic chemists, and has remained beyond reach.[1] It also seems not to occur in the biosynthetic domain. Reported herein is a simple solution of this classical unsolved problem using an approach based on the convergence of three aspects of synthetic chemistry: (1) the use of transition metal mediated C–C coupling, (2) methodology for the formation of C–chiral organolithium reagents, and (3) the idea of accelerating reductive elimination by electron removal. The rational application of transition metal chemistry has transformed the ways in which organic molecules are constructed over the past 5–6 decades, especially using as metals Ni, Ru, Rh and Pd to generate a C–C bond by reductive olefin forming elimination.

This mode of coupling requires that competing pathways such as olefin-forming *β*-hydrogen elimination, free radical formation by homolysis of R–M and stereo-mutation/rearrangement do not intervene. For this reason, acceleration of reductive elimination is important.

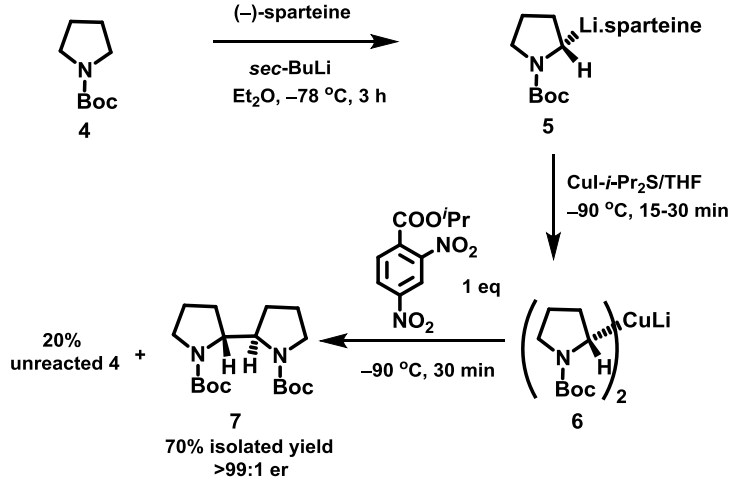
The methodology for accessing C-chiral organolithium reagents which now exists is largely due to the cumulative studies of several groups using complexes of R–Li with chiral diamines, especially sparteine, as controllers for the enantioselective C–H → C–Li metalation.[2-8] We selected the readily available (*S*)-2-lithio derivative of *N*-*tert*-butyloxycarbonyl (Boc) pyrrolidine[5] as the substrate for the initial C(sp³)–C(sp³) coupling studies which are described in detail herein. We also chose copper as the transition metal to effect C–C bond formation, partly because the use of this metal has a long and impressive history for achiral (sp³)–(sp²) and (sp³)–(sp³) coupling.[9] In addition copper is considerably less prone to *β*-hydrogen elimination to form Cu–H and C=C, e.g. as indicated by the relative stability of intermediates such as *t*-Bu–Cu and the mixed cuprate (*t*-Bu)(*n*-Bu)CuLi, the second of which can be made and used in conjugate addition to *α*,*β*-enones.[10] The choice of copper was further indicated by the general availability of Gilman cuprate reagents of the type $(R–Cu–R)^-M^+$. We were also guided by the concept that the required reductive elimination of $(R–Cu–R)^-$ could be enormously accelerated by the effective removal of *two* electrons. In the extreme ease, R–R coupling from the Cu(III) species RCu^+R (or its equivalent) can be expected to be very fast, since it is a close analog of $R^+ + RCu \rightarrow R–R + Cu^+$. Some years ago, we reported the isolation of an adduct of Me_2CuLi and 2-cyclohexenone (at –20 °C or below), **1a**/**1** which was instantly transformed either into **2** or **3** as shown in equation (1).[11,12] The TMS–Cl accelerated and extremely rapid reductive elimination leading to **2** accords with the expectation that removal of electron density by any means

Scheme 1. Conjugate Addition of Me_2CuLi to 2-Cyclohexenone



should accelerate reductive elimination. In the extreme case of RCu^+R the formation of R–R can be energetically similar to an attack of R^+ on R–Cu– which surely would be extremely rapid.[12]

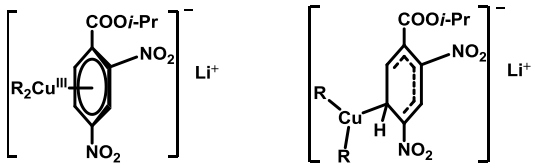
Scheme 2. Enantioselective Lithiation of 4 and C(sp³)–C(sp³) Coupling



The above considerations led to a highly successful enantioselective coupling reaction of **5**, (from *N*-Boc pyrrolidine, **4**) to form the (*R,R*)-coupling product **7** using (–)-sparteine as ligand for the lithiation **4** → **5**, as summarized in

Scheme 2. The chiral lithiated substrate **5** was generated in ether by the method of Beak *et al.*[5] at –78 °C and then converted to the soluble homocuprate **6** at –90 °C by treatment with a concentrated solution of CuI and isopropyl sulfide (1:3) in THF.[14] Slow addition of a cold solution of *i*-propyl 2,4-dinitrobenzoate (2,4-PDB) in THF to the –90 °C solution of the cuprate **6** led to an extremely rapid and highly exothermic reaction to produce **7**. The very fast rate of reaction was evident by an instantaneous color change (to dark red brown) and heat evolution as 2,4-PDB was added. Two experimental variables are especially important for the successful enantioselective formation of the coupling product **7**, including: (1) limiting the time for formation of the cuprate **6** to the minimum necessary and (2) controlling the temperature during the 2,4-PDB accelerated reductive elimination to avoid homolytic cleavage or decomposition of **6**. It should be noted that in the past others have attempted the enantioselective conversion **5** to **7** without success under a variety of conditions.[15] The choice of 2,4-PDB a strongly π-electron deficient benzenoid structure with *three* electron-withdrawing groups on the ring was made to ensure rapid removal of negative charge from the cuprate **6** either by *d*–π* donor acceptor coordination to form **8** or Cu–Ar σ-bonding to form **9**.

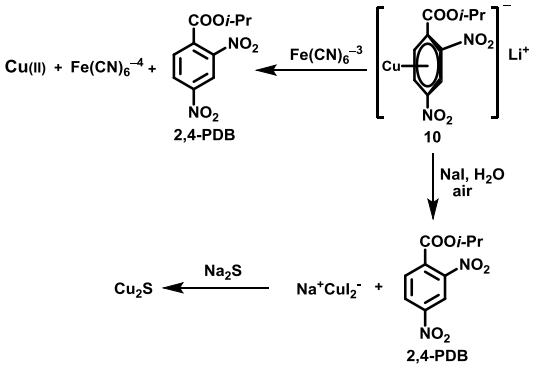
Scheme 3. Reaction of R_2CuLi with 2,4-PDB



8 9

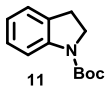
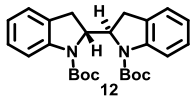
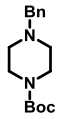
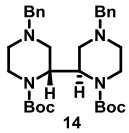
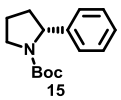
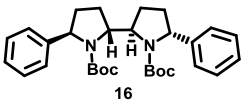
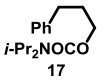
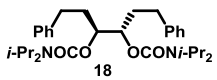
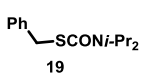
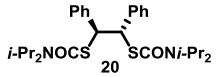
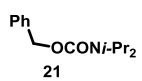
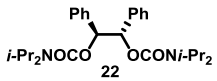
There is insufficient information at this time to allow a decision between their two alternatives. In contrast, however a single electron transfer pathway from **6** to **7** i.e. $R_2Cu^- \rightarrow R_2Cu \rightarrow R–R + Cu(0)$, is inconsistent with the fact that no metallic copper, Cu (0), is produced in the coupling. In addition, one-electron oxidants such as $NO^+BF_4^-$ or ferrocenium tetrafluoroborate do not convert **6** to **7**.[16] When the chiral coupling product **7** is formed from the Cu(III) intermediate **8** or **9**, a complex is formed which we surmise to be the π-donor-acceptor complex **10** (Scheme 4). The intermediate **10** can also be thought of as a Cu^+/π-coordinated 2,4-PDB dianion.

Scheme 4. Putative Intermediate After R–R Coupling of 8



Quenching of **10** with an aqueous solution of NaI containing air generates Cu(I) as $Na^+CuI_2^-$ (100%, quantitative), as determined by the weight of Cu_2S formed after addition of aqueous Na_2S. In addition, the original oxidant 2,4-PDB is recovered unchanged after extractive workup and column chromatography. Quenching of **10** with a solution of $K_3Fe(CN)_6$ also regenerated 2,4-PDB along with the reduction product $K_4Fe(CN)_6$, identified by conversion to Prussian blue, $KFe^{III}[Fe^{II}(CN)_6]$ when treated with $FeCl_3$ in water. These results are summarized in Scheme 4.

Table 1. $C(sp^3)–C(sp^3)$ Coupling of Achiral Reactants (R–H) to Form Chiral Products, R–R

R–H	R–R	Deprotanation Time, Temp	Yield	*er*
 11	 12	6 h, –78 °C	68%	>99:1
 13	 14	5 h, –78 °C	60%	95:5
 15	 16	5 h, –78 °C	60%	94:6
 17	 18	5 h, –78 °C	65%	>99:1
 19	 20	30 min, –90 °C	58%	89:11
 21	 22	1 h, –90 °C	50%	91:9

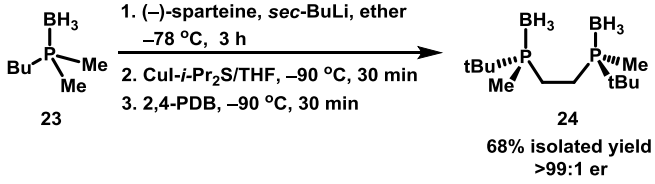
The highly enantioselective transformation of *N*-Boc pyrrolidine (**4**) to the chiral coupling product **7** provides ready access to this useful diamine derivative. We have used the following simple procedure for work up: (1) treatment of the reaction mixture with aqueous acid and separation of the ether phase; (2) basification of the aqueous phase and extraction to recover (–)-sparteine (>95%); (3) concentration of the ether extract and treatment with aqueous base to saponify 2,4-PDB; (4) extraction with ether to give a mixture of unreacted **4** and coupling product **7** which may be separated easily by flash column chromatography on silica gel; and (5) acidification of the aqueous phase to generate 2,4-dinitro benzoic acid. By extending the reaction time for the deprotonation **4** → **5** it is possible to reduce the amount of unreacted **4** that remains after the coupling reaction.

The enantioselective $C(sp^3)–C(sp^3)$ coupling process that is described above and outlined in Scheme 2 has been applied successfully to a variety of other substrates that can be lithiated enantioselectiviely using the (–)-sparteine/*sec*-

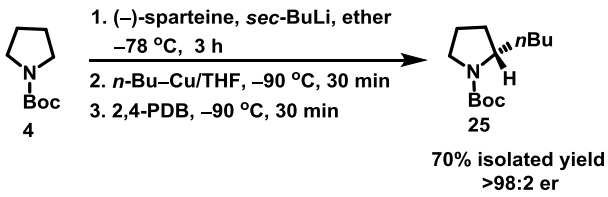
butyllithium reagent. The results for six different types of substrates (**12–22**) are shown in Table 1. We followed previously described procedures for the enantioselective deprotonation of **11**,[17] **13**,[18] **15**,[19] **17**,[20] **19** and **21**.[21, 22] The results summarized in Table 1 demonstrate useful and concise pathways for the synthesis of a variety of C_2-symmetric 1,2 diamines 1,2-diols and 1,2-dithiols.

We have also applied the above C(sp^3)–C(sp^3) coupling process to a variety of other types of substrates, as illustrated by the two examples shown in Scheme 5 and 6. The enantioselective deprotonation of **23**[23] and coupling to **24** demonstrates that primary C(sp^3) stereo centers can also be ligated using the oxidatively accelerated coupling method described herein. The conversion of **4** to **25** illustrates the joining of two different groups to form a hetero-coupling product.

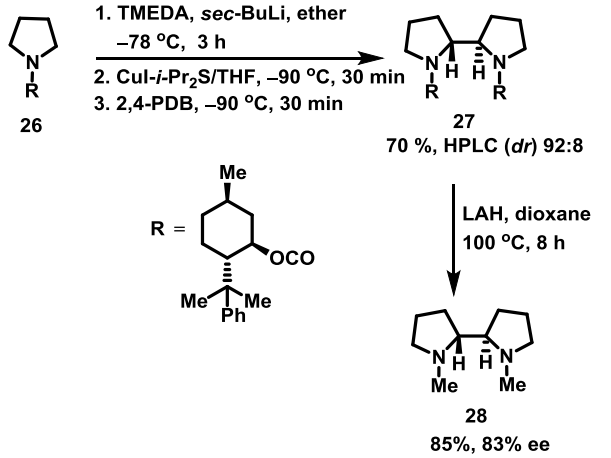
Scheme 5. Primary C(sp^3)–C(sp^3)-Coupling



Scheme 6. Hetero C(sp^3)–C(sp^3)-Coupling



Scheme 7. C(sp^3)–C(sp^3)-Coupling using a Chiral Controller



We also have discovered that the phenmenthyloxy[25] carboxamide of pyrrolidine (**26**) undergoes diastereoselective deprotonation by the *sec*-BuLi–tetramethylethylenediamine (TMEDA) combination to provide after oxidative coupling the diastereomer **27** as the major product. The configuration of **27** was established by reduction using $LiAlH_4$ to the known *R,R*-amine **28**,[24] with recovery of phenmenthol.[25] The enantioselective coupling sequence leading to **28** also demonstrates a novel method for accessing chiral organo-lithium reagents having the metal attached to an sp^3 stereocenter without use of a chiral base.

The formation of C–C bonds via higher valent metal intermediates can also be promoted by the use of electron donating diamines or solvents which stabilize the higher valence state sufficiently to allow access to it, but not so much as to retard reductive elimination. An early example of the latter is the Ni-mediated cross coupling of π-allylnickel halides with alkyl, vinyl or aryl halides in strongly coordinating solvents such as dimethyl formamide.[26] Elegant examples of the former have recently been provided *intra alia* by the groups of G. C Fu[27] and L. M Mirica[28] which have demonstrated useful C–C bond formation reactions via Ni(III).[28] In a similar manner basic ligands facilitate oxidation of Pd (II) to Pd (IV), as dramatically illustrated by the Yu group's discovery that a chiral, strongly electron-supplying bidentate ligand permits oxidation of Pd (II) to Pd (IV) even by I_2, thus accelerating enantioselective C–H insertion and functionalization.[29]

In conclusion, the results described herein a new methodology that is well suited to the generation in a single step of compounds with vicinal stereocenters by copper mediated enantioselective C(sp^3)–C(sp^3) coupling of α-lithiated sp^3 carbons. A critical element in the successful achievement of these coupling reactions is the use of a 2,4-dinitrobenzoate ester to effectively remove electron density from a cuprate, R_2CuLi, by d–π* donor-acceptor complexation to provide a Cu(III) equivalent.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for novel reactions and products including copies of ^{1}H- and ^{13}C-NMR spectra and chiral HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(22) The chiral lithio-derivatives of **19** and **21** lose configuration at an appreciable rate even at –90 °C in ether or toluene and for this reason the enantiomeric purity of the coupling products **20** and **22** is lower than for other examples in Table 1.

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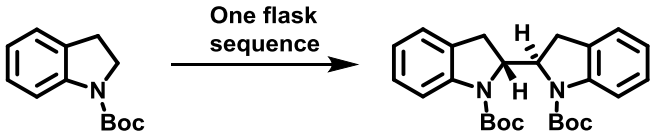

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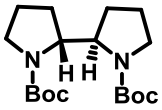
Plus a variety of other examples, including:



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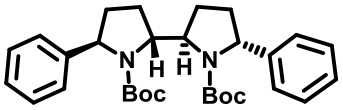

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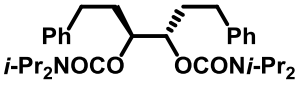

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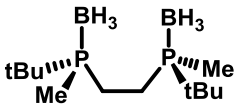

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