

A Journal of the Gesellschaft Deutscher Chemiker A Deutscher Chemiker GDCh International Edition www.angewandte.org

Accepted Article

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.201910397 Angew. Chem. 10.1002/ange.201910397

Link to VoR: http://dx.doi.org/10.1002/anie.201910397 http://dx.doi.org/10.1002/ange.201910397

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Stereoselective C*sp*³-C*sp*² Cross-Couplings of Chiral Secondary Alkylzinc Reagents with Alkenyl and Aryl Halides

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Dedicated to Dr. Klaus Römer on the occasion of his 80th birthday

Abstract: We report palladium-catalyzed cross-coupling reactions of chiral secondary non-stabilized dialkylzinc reagents - prepared from readily available chiral secondary alkyl iodides - with alkenyl and aryl halides. This method provided α -chiral alkenes and arenes with very high retention of configuration (dr up to 98:2) and satisfactory overall yields (up to 76% for 3 reaction steps). The configurational stability of these chiral non-stabilized dialkylzinc reagents was determined and exceeded several hours at 25 °C. DFT-calculations were performed to rationalize the stereoretention during the catalytic cycle. Furthermore, the cross-coupling reaction was applied in an efficient total synthesis of the sesquiterpenes (*S*)- and (*R*)-curcumene with control of the absolute stereochemistry.

Transition-metal-catalyzed cross-coupling reactions are widely used for the construction of complex organic molecules.^[1] Although a range of Csp³-Csp² coupling reactions have been developed, only a few are stereoselective.^[2] In this context, highly stereoretentive cross-couplings of enantioenriched a-chiral alkylzinc reagents are desirable as these reagents are known for their broad functional group tolerance. However, their preparation proved to be challenging since oxidative addition of zinc powder into the carbon-halogen bond proceeds with a loss of stereoinformation.^[2g] A stereoselective palladium-catalyzed cross-coupling reaction after hydroboration of trisubstituted alkenes followed by a boron-zinc exchange reaction has been reported, but proved to be of limited scope.^[3] Lately, a diastereoselective palladium-catalyzed cross-coupling reaction of cyclic alkylzinc reagents, where the stereoselectivity of the crosscoupling is thermodynamically controlled has been reported.^[4] This method leads to high selectivities only with cyclic substrates, which drastically limits the utility of such stereoselective palladium-catalyzed cross-couplings. So far, the preparation of non-stabilized optically pure open-chain organometallic reagents is a challenge for organic synthesis. Recently, we have reported that chiral secondary alkyllithiums 1 can be readily prepared from the corresponding optically enriched a-chiral secondary alkyl iodides 2 via a stereoretentive I/Li-exchange reaction (see Scheme 1). The configurational stability of these secondary alkyllithiums is rather moderate (ca. 1 h at -100 °C in a hexane:ether mixture).^[5] However, transmetalation to the corresponding secondary alkylcopper reagents significantly

[a] J. Skotnitzki, A. Kremsmair, Dr. D. Keefer, Y. Gong, Prof. Dr. R. de Vivie-Riedle, Prof. Dr. P. Knochel Department Chemie, Ludwig-Maximilians-Universität München Butenandtstrasse 5–13, Haus F, 81377 München (Germany) E-mail: paul.knochel@cup.uni-muenchen.de increases this configurational stability (several hours at -50 °C in THF). These chiral alkylcopper organometallics react with activated alkynes, epoxides, 1-bromoalkynes and allylic halides with high retention of configuration.^[6] Furthermore, these organocopper reagents were used in the total synthesis of several pheromones^[6a,6c] with high control of all stereocenters.



Scheme 1. Stereoretentive preparation of secondary alkylzinc reagents 4 and subsequent palladium-catalyzed cross-coupling reaction with alkenyl or aryl halides 5.

Nevertheless, the configurational stability of these chiral secondary alkylcopper reagents is restricted to low temperature reactions. Thus, we envisioned the performance of a stereoretentive transmetalation of chiral alkyllithiums of type 1 with an appropriate ether soluble zinc reagent R'ZnX (3), leading to the mixed dialkylzinc reagents of type 4 (see Scheme 1). These chiral mixed dialkylzinc reagents may undergo a stereoselective palladium-catalyzed cross-coupling with alkenyl and aryl halides of type 5, which would afford α -chiral products of type 6. To achieve such a stereoselective cross-coupling several requirements should be fulfilled: (1) both the transmetalation step (conversion of 7 to 8) and the reductive elimination step (converting 8 to 6) of the catalytic cross-coupling cycle have to be stereoselective; (2) the secondary dialkylzinc reagent 4 must be configurationally stable at the cross-coupling temperature and should contain a group R', which does not easily participate in the catalytic cycle. After several preliminary experiments,^[7] we chose Me₃SiCH₂ZnBr·LiBr (3a) as transmetalating zinc reagent since it is highly soluble in diethyl ether and readily prepared.^[8] To our delight, these conditions allow for the first time a highly stereoselective cross-coupling of chiral non-stabilized open-chain

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secondary alkylzinc reagents with various alkenyl and aryl halides. Hence, we treated the diastereomerically enriched secondary alkyl iodide *syn*-**2a**^[5c] with ^fBuLi (2.2 equiv) in a 3:2 mixture of pentane:diethyl ether at -100 °C for 10 s leading to an intermediate alkyllithium species (see Table 1). Addition of Me₃SiCH₂ZnBr·LiBr (**3a**; 0.95 M in diethyl ether, 1.05 equiv) at -100 °C provided the mixed dialkylzinc species *syn*-**4a**. For performing a subsequent stereoselective palladium-catalyzed cross-coupling, the choice of the palladium catalyst proved to be essential.

Table 1: Optimization for palladium-catalyzed cross-coupling reaction of racemic secondary alkylzinc reagent *syn*-4a.

Ph syn-2a dr = 98:2	1) 'BuLi (inv. add.) (2.2 equiv), -100 °C, 10 s e pentane:ether = 3:2 TMS ZnBr-LiBr 3a (1.05 equiv) -100 °C, 1 min	Me Me Ph Zn TMS syn-4a Syn-4a Catalyst (5 mol%) -n-hex Sa (3.0 equiv) -50 °C to -25 °C, 12 h	Ph
entry	catalyst	yield of <i>syn-6a</i> ^[a]	dr of syn- 6a ^[a]
1	Pd(PPh ₃) ₄	39%	89:11
2	Pd(OAc) ₂ /CPhos	51%	92:8
3	Pd-PEPPSI-iPent	60%	96:4
4	$Pd_2I_2(P^tBu_3)_2$	58%	98:2

[a] The yield and diastereoselectivity (dr; *syn:anti* ratio was determined by GC analysis using dodecane as internal standard.

Addition of 5 mol% $Pd(PPh_3)_4$ and (*E*)-1-iodooct-1-ene (**5a**; 3.0 equiv) as a typical substrate at -50 °C followed by warming to -25 °C and stirring for 12 h at this temperature provided the desired cross-coupling product syn-6a with a diastereoselectivity of syn:anti = 89:11 (entry 1).^[9] Using the catalytic system Pd(OAc)₂/CPhos introduced by Buchwald for the coupling of secondary alkylzinc halides^[10] improved the stereoselectivity of the cross-coupling to syn:anti = 92:8 (entry 2). A further improvement was observed with the NHC-based catalyst Pd-PEPPSI-iPent reported by Organ^[11], which provided the desired product syn-6a with a dr = 96:4 (entry 3). Finally, the Pd(I)-catalyst Pd₂l₂(P^tBu₃)₂ used by Schoenebeck^[12] gave the product syn-6a with complete retention of configuration (entry 4; dr = 98:2). In order to obtain a deeper insight into the configurational stability of these chiral non-stabilized secondary alkylzincs of type 4, we prepared syn-4a at -100 °C and kept it at various temperatures (-50 °C to 25 °C) for a certain time, followed by the stereoselective cross-coupling with 5a, leading to syn-6a (see Table 2). We observed high stability of the zinc species syn-4a up to -10 °C (dr of syn-6a = 97:3). Furthermore, keeping the alkylzinc reagent syn-4a at 25 °C for 1 h and performing a palladiumcatalyzed cross-coupling provided syn-6a with dr = 96:4. However, stirring syn-4a at 25 °C for 4 h led to a minimal epimerization (dr of syn-6a = 89:11). This indicated a high configurational stability of these chiral secondary mixed dialkylzinc reagents (several hours at 25 °C). With this result in hand, we slightly modified the experimental procedure to the effect that the cross-coupling reaction could be performed at room temperature. Under these conditions, Pd-PEPPSI-iPent showed superior results compared

to the Pd(I)-dimer catalyst regarding β -hydride elimination and formation of side products such as dimerization. $^{[7]}$

Table	2.	Stability	of	racemic	secondary	alkylzinc	reagent	syn- 4a	and
subsequent cross-coupling reaction with alkenyl iodide 5a.									

Me I Ph syn-2a dr = 98:	1) ^f BuLi (inv. add.) (2.2 equiv), -100 °C, pentane:ther = 3 2) TMS ZnBr·Li 3a 2 (1.05 equiv) -100 °C , 1 min	10 s :2 Br Ph s time, t	Me 2n TMS syn-4a emperature (3.0 equiv) -50 °C to -25 °C, 12	Me Me Ph+
entry	temperature	time	yield of syn-6a ^[a]	dr of s <i>yn</i> - 6a ^[a]
1	–50 °C	10 min	61%	97:3
2	–30 °C	10 min	58%	97:3
3	−10 °C	10 min	50%	97:3
4	25 °C	60 min	51%	96:4
5	25 °C	240 min	53%	89:11

[a] The yield and diastereoselectivity (dr; syn:*anti* ratio was determined by GC analysis using dodecane as internal standard.

In a typical procedure, the chiral mixed dialkylzinc reagents (4ac) were generated as described above and subsequently warmed to room temperature over 15 min (see Table 3). The dialkylzinc reagent was then added dropwise to a stirring solution of 5 mol% Pd-PEPPSI-iPent and the alkenyl iodide of type 5 (3.0 equiv) in toluene. After stirring for 1 h at room temperature the corresponding α -chiral cross-coupling products were isolated in up to 52% yield and with high retention of configuration (dr up to 98:2). In this way, the stereodefined alkenes syn-6a^[13] and anti-6a were prepared from the corresponding iodides in 43% and 39% yield, respectively (dr = 98:2 and dr = 5:95). Interestingly, the thermodynamically more stable alkylzinc reagent anti-4a afforded the corresponding (E)-alkene anti-6a in lower yield and with less retention of configuration compared to the syn-product. In most other cases a high retention of configuration (dr >94:6) was achieved. Thereby, the (E)/(Z)-configuration of the alkenyl iodides of type 5 turned out to be highly important. All attempts to use (Z)alkenyl iodides as cross-coupling partners were unsuccessful presumably due to steric hindrance in the palladium(II)intermediates 7 and 8.^[7]

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Table 3. Stereoretentive cross-coupling reactions of racemic secondary alkylzinc reagents 4 with alkenyl iodides 5a-f leading to α -chiral alkenes 6a-h.

Me R ¹ I dr = 98:2	1) ¹ BuLi (inv. add.) (2.2 equiv), -100 °C, 10 s pentane:ether = 3:2 2) TMS ZnBr-LiBr (1.05 equiv), -100 °C, 1 min then rt, 15 min	R ¹ Zn TMS	Pd-PEPPSI-iPent (5 mol%) $I \xrightarrow{R^2} R^2$ 5a-f (3.0 equiv) toluene rt, 1 h
entry	alkylzinc	electrophile	product of type 6 ^[a]
1	Ph Ph syn-4a	۱ 5a	Me Me ph <i>syn-</i> 6a , 43%, dr = 98:2
2	Ph — Me Ph — Zn — TMS anti- 4a	5a	Me Me Ph <i>anti-</i> 6a , 39%, dr = 5:95
3	syn- 4a	5b	Me Me Ph + + + + + + + + + + + + + + + + + + +
4	syn- 4a	5c	Me Me Ph
5	syn- 4a	Me Me 5d	Me Me PhOTMS Me Me syn-6d, 39%, dr = 94:6
6	syn -4a	CI 5e	Me Me Ph Cl syn-6e, 44%, dr = 98:2
7	syn -4a	OBn 5f	Me Me Ph syn-6f, 43%, dr = 96:4
8	TBSO syn-4b	۱5a	Me Me TBSO
9	Me Me syn-4c	5a	Me <i>Me n</i> -hex <i>Me</i> <i>syn-6h</i> , 46% yield, dr = 96:4

[a] The diastereoselectivity (dr; syn:anti ratio) was determined by ¹H-NMR spectroscopy and GC analysis.

These conditions were broadly applicable. Hence, we performed such a cross-coupling reaction with other secondary alkylzinc reagents **4b-c** (see entry 9 and 10). The 1,3-functionalized secondary alkyl iodide *rac-2b* was prepared according to literature procedure, followed by an I/Li-exchange reaction, which after epimerization (-50 °C, 30 min) led to the chelate-stabilized lithium species.^[5c] Subsequent transmetalation to the corresponding dialkylzinc reagent *syn-4b* followed by cross-coupling with **5a** afforded the silyl-protected alkene *syn-6g* in 43% yield (dr = 93:7). Furthermore, the 1,4-functionalized dialkylzinc reagent *syn-4c* was suitable for cross-coupling reaction leading to *syn-6h* in 46% yield and dr = 96:4.

As many pharmaceuticals and natural products contain aromatic moieties, the preparation of chiral arenes and heteroarenes is of great interest. Thus, we extended our method to palladium-catalyzed cross-couplings with aryl bromides of type **9** leading to the corresponding chiral arenes and heteroarenes (see Scheme 2). Various aryl bromides with electron donating and electron

withdrawing substituents were used, leading to products 6i-n (38-59% yield; dr up to 98:2). Thus, the cross-coupling reaction of syn-4a with bromothiophene derivatives^[14] afforded syn-6k-I in 38-59% yield and with high retention of configuration (dr up to 98:2). In addition, 1-bromonaphthalene was used for the cross-coupling reaction with the dialkylzinc reagents syn-4a and syn-4c leading to α-chiral naphthalenes syn-6j and syn-6m in good yields (51-56% yield) and high stereoretention (dr up to 97:3). This crosscoupling was also extended to optically enriched alkylzinc reagents leading to the corresponding α -chiral arenes (R)-60, (S)-**60** and (*R*)-**6p** (up to 76% yield, er = 91:9).^[15] To demonstrate the synthetic utility of the method, we performed the natural product synthesis of the two enantiomers of α -curcumene **10**, an aromatic sesquiterpene.^[16] Both enantiomers can be found in nature, e.g. in essential oils or in the pheromone produced by the red-shoulder stink bug.^[17] Starting from the readily available chiral secondary alkyl iodide (S)- or (R)-2d,^[6a] the corresponding chiral secondary alkylzinc reagents (S)- or (R)-4d were prepared. Subsequent palladium-catalyzed cross-coupling reaction with 4-bromotoluene afforded the natural products (S)-curcumene ((S)-10; 50% yield; er = 93:7) and (R)-curcumene ((R)-10; 46% yield; er = 7:93).





Furthermore, DFT-calculations were performed to gain insight into the high retention of configuration of secondary alkylzinc reagents. Therefore, the configurational stability of the chiral alkylzinc reagents *syn*-**4a** and *anti*-**4a** was investigated. Solvation effects were accounted for by the *Polarizable Continuum Model* (PCM) as well as by explicit treatment with diethyl ether molecules.^[18] Comparison of the free energies between the two isomers showed that *anti*-**4a** is thermodynamically more stable than the corresponding alkylzinc reagent *syn*-**4a** ($\Delta G = +2.7$ kcal/mol). Coordination of one solvent molecule (diethyl ether) to the zinc site leads to a marginal rise of energy both for *syn*-**4a** and

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anti-4a, which suggests that solvent coordination is not relevant for the epimerization pathway. This result is in agreement with the fact that the cross-coupling reaction proceeded also in other solvents, such as toluene or THF, with high retention of configuration.^[7] We examined two possible pathways, which could lead to epimerization from syn-4a to anti-4a and vice versa, namely via a planar transition state ts-4a (see Scheme 3) or by cleavage of the carbon-zinc bond. Both the transition state energy of 95.5 kcal/mol and the carbon-zinc bond energy of ca. 35 kcal/mol corroborate the high stability of 4a towards epimerization at 25 °C. Another important step in this catalytic cross-coupling cycle, where stereoretention is crucial, is the configurational stability of the Pd(II)-intermediate 8 (see Scheme 1). We performed an analogous analysis of potential epimerization channels on 8 using Pd-PEPPSI. To stay within the computational feasibility of our quantum chemical method, we simplified the catalyst by replacing the four experimentally used isopentyl residues in Pd-PEPPSI-iPent with methyl groups. This allows slightly more steric flexibility, while the electronic nature around the Pd(II) and the carbon stereocenter is unaltered. Starting from a tetrahedral geometry of the four ligands around the Pd(II) center, the optimization ends in an energetic minimum which exhibits a nearly planar tetragonal structure.^[18] Thus, there are four possible species for 8, with either the syn- or the anti-isomer in cis (8a) or trans (8b) position to the alkene (see Scheme 3). A comparison of configurational stabilities of the four species showed that the cis-conformer 8a is more stable than the trans-conformer 8b, which is encouraging since reductive elimination can only occur from the cis-configuration 8a.



Scheme 3. Theoretical calculations of the epimerization of secondary alkylzinc reagent *anti*-4a to *syn*-4a and Pd(II)-intermediates of type 8. Molecular geometries and Gibbs free energies ΔG_{solv} in solution. **Top:** Stabilities of *anti*-4a and *syn*-4a. Bottom: Stabilities of *syn*- and *anti*-8a and 8b.

With respect to the finding of our study again the high energy of the transition states *ts*-**8a** (41.8 kcal/mol; *anti*-**8a** to *syn*-**8a**) and *ts*-**8b** (39.7 kcal/mol; *anti*-**8b** to *syn*-**8b**) and carbon-palladium bonding energies of *syn*-**8a** (47.7 kcal/mol), *anti*-**8a** (47.2 kcal/mol), *syn*-**8b** (41.6 kcal/mol), and *anti*-**8b** (40.1 kcal/mol) corroborate the experimentally found retention of configuration.

Interestingly, the energy barrier is significantly lower for *ts*-**8a** and *ts*-**8b** than it is for *ts*-**4a**, which suggests that a potential loss of stereoinformation occurs more likely at the Pd(II)-intermediate **8**. Nevertheless, we presume that the minimal epimerization of the secondary alkylzinc reagents may be due to polymolecular exchange reactions between these zinc reagents, which may involve the salts LiBr and LiI.

In summary, we have shown that chiral non-stabilized dialkylzinc reagents can be prepared via an l/Li-exchange reaction and subsequent transmetalation with Me₃SiCH₂ZnBr-LiBr (**3a**) with high retention of the configuration. These chiral dialkylzincs are configurationally stable at room temperature for at least four hours and undergo Csp^3-Csp^2 cross-coupling reactions with various alkenyl and aryl halides, leading to α -chiral alkenes and arenes with high stereoretention. DFT-calculations were performed to explain the high stability of the chiral dialkylzincs and the retention of configuration during the catalytic cycle. Additionally, this method was used for the preparation of (*S*)- and (*R*)- α -curcumene **10** in good enantioselectivity. Further mechanistic studies and applications are currently under investigation in our laboratories.

Experimental Section

See Supporting Information.

Author Contributions

[‡]J. Skotnitzki and A. Kremsmair contributed equally.

Acknowledgements

We thank the SFB749 for financial support. We also thank Albemarle for the generous gift of chemicals. J. S. thanks the FCI-foundation for a fellowship.

Keywords: cross-coupling • lithium • palladium • zinc • natural products

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Chiral couplings made easy: Chiral secondary alkylzinc reagents underwent stereoselective palladium-catalyzed cross-coupling reactions with alkenyl and aryl halides. These chiral mixed dialkylzincs are configurationally stable at room temperature for several hours. DFT-calculations were performed to rationalize the overall retention in the catalytic cycle. This method was applied in the total synthesis of the sesquiterpenes (*S*)- and (*R*)-curcumene.

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