**Abstract:** We report palladium-catalyzed cross-coupling reactions of chiral secondary non-stabilized dialkylzinc reagents, prepared from readily available chiral secondary alkyl iodides, with alkelyl and aryl halides. This method provides 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)-cyclocurtcumene with control of the absolute stereochemistry.

Transition-metal-catalyzed cross-coupling reactions are widely used for the construction of complex organic molecules. Although a range of Csp\(^3\)-Csp\(^2\) coupling reactions have been developed, only a few are stereoselective. In this context, highly stereoretentive cross-couplings of enantioenriched α-chiral alkylzinc reagents are desirable since 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. 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. Lately, a diastereoselective palladium-catalyzed cross-coupling reaction of cyclic alkylzinc reagents, where the stereoselectivity of the cross-coupling is thermodynamically controlled, has been reported. This method leads to high selectivity 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 alkylithiums can be readily prepared from the corresponding optically enriched α-chiral secondary alkyl iodides through a stereoretentive I/Li exchange reaction. We envision the performance of this method leads to high selectivity 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 alkylithiums can be readily prepared from the corresponding optically enriched α-chiral secondary alkyl iodides through a stereoretentive I/Li exchange reaction. The configurational stability of these secondary alkylithiums is rather moderate (ca. 1 h at –100°C in a hexane/ether mixture). However, transmetalation to the corresponding secondary alkylcopper reagents significantly increases this configurational stability (several hours at –50°C in THF). These chiral alkylcopper organometallics react with activated alkenes, epoxides, 1-bromoalkynes, and allylic halides with high retention of configuration. Furthermore, these organocopper reagents were used in the total synthesis of several pheromones with high control of all stereocenters.

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 alkylolithiums 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 alk enyl and aryl halides of type 5, which would afford 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 into 6) of the catalytic cyclic coupling cycle have to be stereoselective; 2) the secondary dialkylzinc reagent 4 must be configurationally stable at the cross-coupling temperature and should contain an R’ group that does not easily participate in the reductive elimination step (converting 8 into 6).

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.

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

| Entry | Temperature [°C] | Time [min] | Yield of syn-6a[^a] | dr of syn-6a[^a] |
|-------|-----------------|------------|---------------------|-----------------|
| 1     | –50             | 10         | 61%                 | 97:3            |
| 2     | –30             | 10         | 58%                 | 97:3            |
| 3     | –10             | 10         | 50%                 | 97:3            |
| 4     | 25°C            | 60         | 51%                 | 96:4            |
| 5     | 25°C            | 240        | 53%                 | 89:11           |

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

Addition of 5 mol % Pd(PPh3)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). Using the catalytic system Pd(OAc)2/CPhos introduced by Buchwald for the coupling of secondary alkylzinc halides[8] 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,[9] which provided the desired product syn-6a with a dr = 96:4 (entry 3). Finally, the Pd3-catalyst Pd3I4(PBu3)2 used by Schoenebeck[12] gave the product anti-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.

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

| Entry | Catalyst | Yield of syn-6a[^b] | dr of syn-6a[^b] |
|-------|----------|---------------------|-----------------|
| 1     | Pd(PPh3)4 | 39%                 | 89:11           |
| 2     | Pd(OAc)2/CPhos | 51% | 92:8            |
| 3     | Pd-PEPPSI-Ipent | 60% | 96:4            |
| 4     | Pd3I4(PBu3)2 | 58% | 98:2            |

[^b]: 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 (4a–c) 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 alkyl 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 alkynes 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 alkyl iodides of type 5 turned out to be highly important. All attempts to use Z-alkyl iodides as cross-coupling partners were unsuccessful presumably due to...
Comparison of the free
To demonstrate the synthetic utility of the
leading to the corresponding chiral arenes
starting from the readily available chiral alkylzinc reagents with alkenyl iodides afforded racemic secondary alkylzinc reagents 4 with aryl bromides 9, leading to α-chiral arenes and heteroarenes (6a–h).

| Entry | Alkylzinc | Electrophile | Product of type 6[a] |
|-------|-----------|--------------|---------------------|
| 1     | syn-4a    | Ph-H         | 6a                  |
| 2     | syn-4a    | Ph-H         | 6a                  |
| 3     | syn-4a    | Ph-H         | 6a                  |
| 4     | syn-4a    | Ph-H         | 6a                  |
| 5     | syn-4a    | Ph-H         | 6a                  |
| 6     | syn-4a    | Ph-H         | 6a                  |
| 7     | syn-4a    | Ph-H         | 6a                  |
| 8     | syn-4a    | Ph-H         | 6a                  |
| 9     | syn-4a    | Ph-H         | 6a                  |

[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 entries 8 and 9). The 1,3-functionalized secondary alkyl iodide rac-2b was prepared according to a reported procedure, followed by an I/Li-exchange reaction, which after epimerization (−50°C, 30 min) led to the chelate-stabilized lithium species. Subsequent transmetallation 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-4e was suitable for cross-coupling, leading to syn-6h in 46% yield and dr = 96:4.

Since 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). The cross-coupling reaction of syn-4a with bromothiophene derivatives afforded syn-6l 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 cross-coupling was also extended to optically enriched alkylzinc reagents, leading to the corresponding α-chiral arenes (R)-6o, (S)-6o, and (R)-6p (up to 76% yield, er = 91:9). To demonstrate the synthetic utility of the method, we performed natural product synthesis of the two enantiomers of α-curcumene (10), an aromatic sesquiterpene. Both enantiomers can be found in nature, for example, in essential oils or in the pheromone produced by the red-shoulder stink bug. Starting from the readily available chiral secondary alkyl iodide (S)- or (R)-2d, 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. Comparison of the free
energies between the two isomers showed that \textit{anti}-4a is thermodynamically more stable than the corresponding alkylzinc reagent \textit{syn}-4a ($\Delta G = +2.7 \text{kcal mol}^{-1}$). Coordination of one solvent molecule (diethyl ether) to the zinc site leads to a marginal rise of energy both for \textit{syn}-4a and \textit{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 also proceeded in other solvents, such as toluene or THF, with high retention of configuration.\cite{7} We examined two possible pathways that could lead to epimerization from \textit{syn}-4a to \textit{anti}-4a and vice versa, namely via a planar transition state \textit{ts}-4a (see Scheme 3) or through cleavage of the carbon–zinc bond.

\begin{equation}
\Delta G_{\text{cis}} = \Delta G_{\text{trans}} \pm 2.7 \text{kcal mol}^{-1}
\end{equation}

\begin{equation}
\Delta G_{\text{trans}} = \Delta G_{\text{cis}} \pm 2.7 \text{kcal mol}^{-1}
\end{equation}

\textbf{Scheme 3.} Theoretical calculations of the epimerization of secondary alkylzinc reagent \textit{anti}-4a to \textit{syn}-4a and Pd\textsuperscript{II} intermediates of type 8. Molecular geometries and Gibbs free energies $\Delta G_{\text{cis\_sol}}$ in solution. Top: Stabilities of \textit{anti}-4a and \textit{syn}-4a. Bottom: Stabilities of \textit{syn}- and \textit{anti}-8a and 8b.

Both the transition-state energy of 95.9 kcal mol$^{-1}$ and the carbon–zinc bond energy of ca. 35 kcal mol$^{-1}$ 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\textsuperscript{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-$\beta$Pent with methyl groups. This allows slightly more steric flexibility, while the electronic nature around the Pd\textsuperscript{II} and the carbon stereocenter is unaltered. Starting from a tetrahedral geometry of the four ligands around the Pd\textsuperscript{II} center, the optimization ends in an energetic minimum that exhibits a nearly planar tetragonal structure.\cite{10} Thus, there are four possible species for 8, with either the \textit{syn} or the \textit{anti} isomer in \textit{cis} (8a) or \textit{trans} (8b) position to the alkene (see Scheme 3). A comparison of configurational stabilities of the four species showed that the \textit{cis} conformer 8a is more stable than the \textit{trans} conformer 8b, which is encouraging since reductive elimination can only occur from the \textit{cis} configuration 8a.

Once again, the calculated high energy of the transition states ts-8a (41.8 kcal mol$^{-1}$; \textit{anti}-8a to \textit{syn}-8a) and ts-8b (39.7 kcal mol$^{-1}$; \textit{anti}-8b to \textit{syn}-8b) and carbon–palladium bonding energies of \textit{syn}-8a (47.7 kcal mol$^{-1}$), \textit{anti}-8a (47.2 kcal mol$^{-1}$), \textit{syn}-8b (41.6 kcal mol$^{-1}$), and \textit{anti}-8b (40.1 kcal mol$^{-1}$) 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 is more likely to occur at the Pd\textsuperscript{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 through an I/Li-exchange reaction and subsequent transmetalation with Me\textsubscript{3}SiCH\textsubscript{2}ZnBr-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\textsuperscript{3}–Csp\textsuperscript{3} cross-coupling reactions with various alkyl and aryl halides, leading to $\alpha$-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)-$\alpha$-curcumene (10) with good enantioselectivity. Further mechanistic studies and applications are currently under investigation in our laboratories.

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\section*{Conflict of interest}

The authors declare no conflict of interest.

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