

## Cross-Coupling

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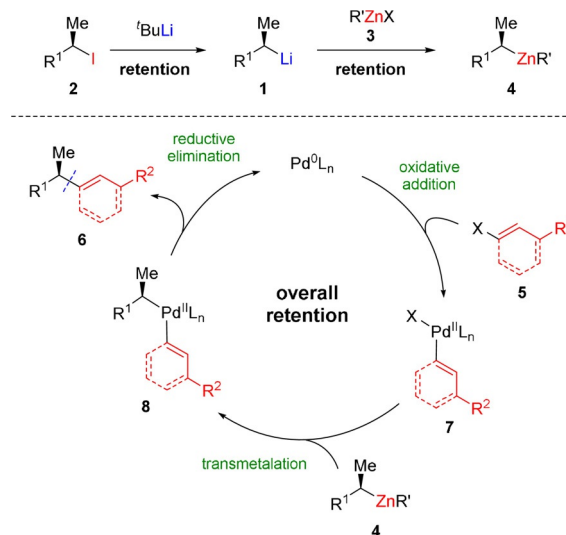
Stereoselective Csp<sup>3</sup>–Csp<sup>2</sup> Cross-Couplings of Chiral Secondary Alkylzinc Reagents with Alkenyl and Aryl HalidesJuri Skotnitzki<sup>†</sup>, Alexander Kremsmair<sup>†</sup>, Daniel Keefer, Ye Gong, Regina de Vivie-Riedle, and Paul Knochel\*

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 provides  $\alpha$ -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.<sup>[1]</sup> Although a range of Csp<sup>3</sup>–Csp<sup>2</sup> coupling reactions have been developed, only a few are stereoselective.<sup>[2]</sup> In this context, highly stereoretentive cross-couplings of enantioenriched  $\alpha$ -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.<sup>[2g]</sup> 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.<sup>[3]</sup> 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.<sup>[4]</sup> 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 alkylzinc reagents **1** can be readily prepared from the corresponding optically enriched  $\alpha$ -chiral secondary alkyl iodides **2** through a stereoretentive I/Li exchange reaction (see Scheme 1). The configurational sta-



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

bility of these secondary alkylzinc reagents is rather moderate (ca. 1 h at  $-100^{\circ}\text{C}$  in a hexane/ether mixture).<sup>[5]</sup> However, transmetalation to the corresponding secondary alkylcopper reagents significantly increases this configurational stability (several hours at  $-50^{\circ}\text{C}$  in THF). These chiral alkylcopper organometallics react with activated alkynes, epoxides, 1-bromoalkynes, and allylic halides with high retention of configuration.<sup>[6]</sup> Furthermore, these organocopper reagents were used in the total synthesis of several pheromones<sup>[6a,c]</sup> 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

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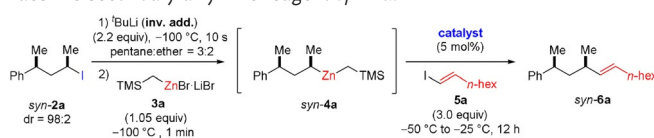
[†] These authors contributed equally to this work.

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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 alkenyl and aryl halides of type **5**, which would afford  $\alpha$ -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 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 an R' group that does not easily participate in the catalytic cycle. After several preliminary experiments,<sup>[7]</sup> we chose Me<sub>3</sub>SiCH<sub>2</sub>ZnBr·LiBr (**3a**) as a transmetalating zinc reagent since it is highly soluble in diethyl ether and readily prepared.<sup>[8]</sup> To our delight, these conditions allow for the first time a highly stereoselective cross-coupling of chiral non-stabilized open-chain secondary alkylzinc reagents with various alkenyl and aryl halides. Hence, we treated the diastereomerically enriched secondary alkyl iodide *syn*-**2a**<sup>[5c]</sup> with <sup>t</sup>BuLi (2.2 equiv) in a 3:2 mixture of pentane/diethyl ether at  $-100^\circ\text{C}$  for 10 s leading to an intermediate alkylolithium species (see Table 1). Addition of Me<sub>3</sub>SiCH<sub>2</sub>ZnBr·LiBr (**3a**; 0.95 M in diethyl ether, 1.05 equiv) at  $-100^\circ\text{C}$  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**.



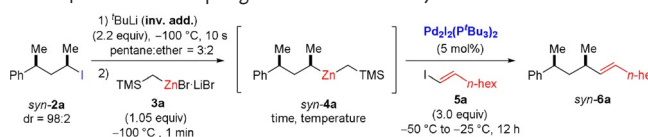
Entry	Catalyst	Yield of <i>syn</i> - <b>6a</b> <sup>[a]</sup>	dr of <i>syn</i> - <b>6a</b> <sup>[a]</sup>
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	39%	89:11
2	Pd(OAc) <sub>2</sub> /CPhos	51%	92:8
3	Pd-PEPPSI-iPent	60%	96:4
4	Pd <sub>2</sub> I <sub>2</sub> (P <sup>t</sup> Bu <sub>3</sub> ) <sub>2</sub>	58%	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<sub>3</sub>)<sub>4</sub> and (*E*)-1-iodooct-1-ene (**5a**; 3.0 equiv) as a typical substrate at  $-50^\circ\text{C}$  followed by warming to  $-25^\circ\text{C}$  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).<sup>[9]</sup> Using the catalytic system Pd(OAc)<sub>2</sub>/CPhos introduced by Buchwald for the coupling of secondary alkylzinc halides<sup>[10]</sup> 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,<sup>[11]</sup> which provided the desired product *syn*-**6a** with a dr = 96:4 (entry 3). Finally, the Pd<sup>I</sup>-catalyst Pd<sub>2</sub>I<sub>2</sub>(P<sup>t</sup>Bu<sub>3</sub>)<sub>2</sub> used by

Schoenebeck<sup>[12]</sup> 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  $-100^\circ\text{C}$  and kept it at various temperatures ( $-50^\circ\text{C}$  to  $25^\circ\text{C}$ ) 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 alkenyl iodide **5a**.



Entry	Temperature [°C]	Time [min]	Yield of <i>syn</i> - <b>6a</b> <sup>[a]</sup>	dr of <i>syn</i> - <b>6a</b> <sup>[a]</sup>
1	$-50$	10	61%	97:3
2	$-30$	10	58%	97:3
3	$-10$	10	50%	97:3
4	$25^\circ\text{C}$	60	51%	96:4
5	$25^\circ\text{C}$	240	53%	89:11

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

up to  $-10^\circ\text{C}$  (dr of *syn*-**6a** = 97:3). Furthermore, keeping the alkylzinc reagent *syn*-**4a** at  $25^\circ\text{C}$  for 1 h and performing a palladium-catalyzed cross-coupling provided *syn*-**6a** with dr = 96:4. However, stirring *syn*-**4a** at  $25^\circ\text{C}$  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  $25^\circ\text{C}$ ). With this result in hand, we slightly modified the experimental procedure so that the cross-coupling reaction could be performed at room temperature. Under these conditions, Pd-PEPPSI-iPent showed superior results compared to the Pd<sup>I</sup>-dimer catalyst regarding  $\beta$ -hydride elimination and the formation of side products such as dimerization.<sup>[7]</sup>

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 alkenyl iodide of type **5** (3.0 equiv) in toluene. After stirring for 1 h at room temperature, the corresponding  $\alpha$ -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**<sup>[13]</sup> 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

**Table 3:** Stereoretentive cross-coupling reactions of racemic secondary alkylzinc reagents **4** with alkenyl iodides **5a–f** leading to  $\alpha$ -chiral alkenes **6a–h**.

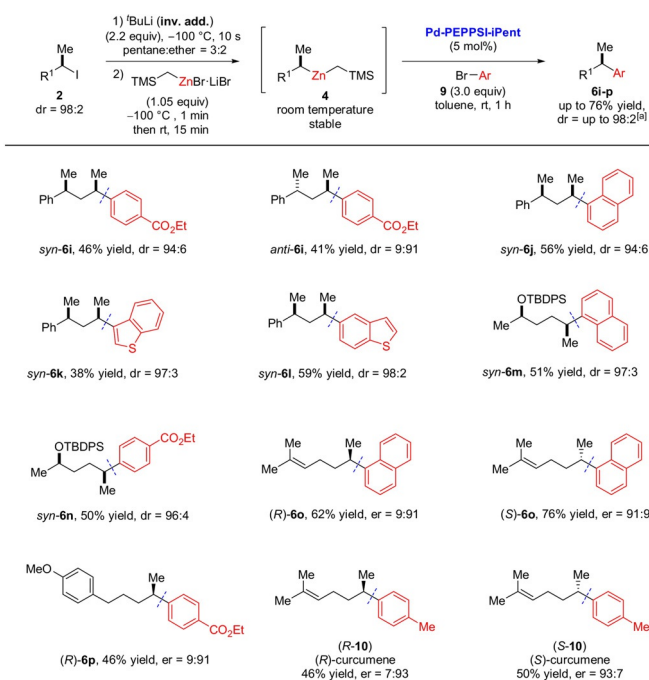
Entry	Alkylzinc	Electrophile	Product of type <b>6</b> <sup>[a]</sup>
1			
2			
3			
4			
5			
6			
7			
8			
9			

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

to steric hindrance in the palladium(II)-intermediates **7** and **8**.<sup>[7]</sup>

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.<sup>[5c]</sup> 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, 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 bro-

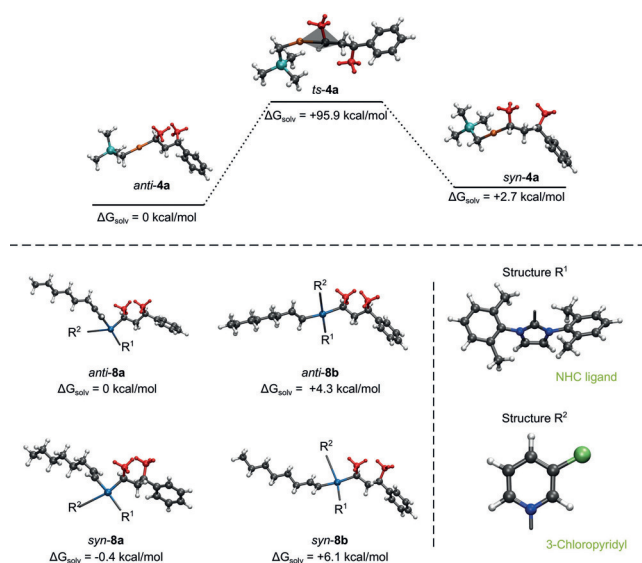


**Scheme 2.** Cross-coupling reaction of chiral alkylzinc reagents **4** with aryl bromides **9**, leading to  $\alpha$ -chiral arenes and heteroarenes (**6i–p**). [a] The diastereoselectivity (dr; *syn/anti* ratio) was determined by <sup>1</sup>H-NMR spectroscopy and GC analysis.

mides 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<sup>[14]</sup> afforded *syn*-**6k,l** 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  $\alpha$ -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  $\alpha$ -chiral arenes (*R*)-**6o**, (*S*)-**6o**, and (*R*)-**6p** (up to 76% yield, er = 91:9).<sup>[15]</sup> To demonstrate the synthetic utility of the method, we performed natural product synthesis of the two enantiomers of  $\alpha$ -curcumene (**10**), an aromatic sesquiterpene.<sup>[16]</sup> Both enantiomers can be found in nature, for example, in essential oils or in the pheromone produced by the red-shoulder stink bug.<sup>[17]</sup> Starting from the readily available chiral secondary alkyl iodide (*S*)- or (*R*)-**2d**,<sup>[6a]</sup> 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.<sup>[18]</sup> 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<sup>-1</sup>). Coordination of one solvent molecule (diethyl ether) to the zinc site leads to a marginal rise of energy both for *syn*-**4a** and *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.<sup>[7]</sup> We examined two possible pathways that 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 through cleavage of the carbon–zinc bond.



**Scheme 3.** Theoretical calculations of the epimerization of secondary alkylzinc reagent *anti*-**4a** to *syn*-**4a** and Pd<sup>II</sup> intermediates of type **8**. Molecular geometries and Gibbs free energies  $\Delta G_{\text{solv}}$  in solution. Top: Stabilities of *anti*-**4a** and *syn*-**4a**. Bottom: Stabilities of *syn*- and *anti*-**8a** and **8b**.

Both the transition-state energy of 95.9 kcal mol<sup>-1</sup> and the carbon–zinc bond energy of ca. 35 kcal mol<sup>-1</sup> 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<sup>II</sup> 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<sup>II</sup> and the carbon stereocenter is unaltered. Starting from a tetrahedral geometry of the four ligands around the Pd<sup>II</sup> center, the optimization ends in an energetic minimum that exhibits a nearly planar tetragonal structure.<sup>[18]</sup> 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**.

Once again, the calculated high energy of the transition states *ts*-**8a** (41.8 kcal mol<sup>-1</sup>; *anti*-**8a** to *syn*-**8a**) and *ts*-**8b** (39.7 kcal mol<sup>-1</sup>; *anti*-**8b** to *syn*-**8b**) and carbon–palladium bonding energies of *syn*-**8a** (47.7 kcal mol<sup>-1</sup>), *anti*-**8a** (47.2 kcal mol<sup>-1</sup>), *syn*-**8b** (41.6 kcal mol<sup>-1</sup>), and *anti*-**8b** (40.1 kcal mol<sup>-1</sup>) 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<sup>II</sup> 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<sub>3</sub>SiCH<sub>2</sub>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<sup>3</sup>–Csp<sup>2</sup> cross-coupling reactions with various alkenyl 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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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** cross-coupling · lithium · natural products · palladium · zinc

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