Stereoselective Cross-Coupling

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Highly Diastereoselective C(sp^3)–C(sp) Cross-Coupling Reactions between 1,3- and 1,4-Substituted Cyclohexylzinc Reagents and Bromoalkynes through Remote Stereocontrol**

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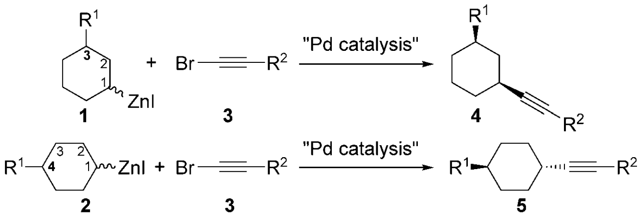
Alkynes are found in a vast array of natural products and bioactive molecules,[1] and make up important constituents in many functional materials,[1c,2] including liquid crystals,[3] dyes,[4] and organic light-emitting diodes (OLEDs).[5] Therefore, the development of novel methods that allow an efficient and stereoselective introduction of the alkynyl unit into organic molecules is highly desirable. Whereas the Sonogashira reaction[6] has been well established for the construction of C(sp)–C(sp^2) bonds, far fewer synthetic methods are available for the coupling between a C(sp^3) and a C(sp) center.[7–10] The C–C bond formation is problematic in such reactions due to competing β-hydride elimination and sluggish reductive elimination.[7] Most of the existing procedures are based on the coupling of an organometallic alkynyl compound or alkyne with an alkyl halide.[8] Useful transition-metal-catalyzed coupling reactions involving organometallic alkyl compounds have evolved only recently.[9] Such methods include oxidative coupling of primary alkylzinc reagents with terminal alkynes[9a] or alkynylstannanes,[9b,c] as well as the copper-catalyzed coupling of alkylmagnesium reagents with alkynyl halides.[9d] Palladium- and copper-catalyzed decarboxylative coupling reactions may also be used.[10] Stereoselective versions of these reactions are scarce and have so far only been developed for C(sp)–C(sp^3) coupling reactions.[8f,g]

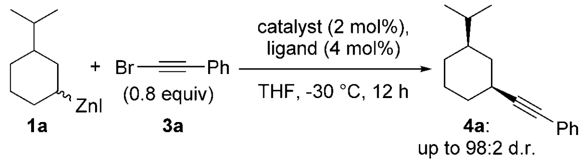
Recently, we showed that palladium catalysis allows highly diastereoselective C(sp^3)–C(sp^2) Negishi cross-coupling reactions between substituted cycloalkylzinc species and aryl or heteroaryl halides.[11] Thereby, a remote diastereocontrol was observed for various 3- and even 4-substituted cyclohexylzinc reagents. We envisioned that a related cross-coupling between these cyclohexylzinc reagents (**1** or **2**) and alkynyl bromides (**3**) could be achieved and would provide stereochemically defined alkynes of type **4** and **5** with 1,3- or 1,4-remote stereocontrol (Scheme 1).

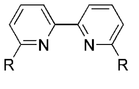
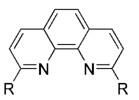


Scheme 1. Diastereoselective C(sp^3)–C(sp) coupling of substituted cyclohexylzinc reagents with remote stereocontrol.

In a preliminary experiment we treated the 3-substituted cyclohexylzinc reagent **1a**—obtained by zinc insertion in the presence of LiCl[12]—with 1-bromophenylacetylene[13] (**3a**) in THF in the presence of different catalysts (Table 1). With 10 mol% CuCN·2LiCl,[14] the expected cross-coupling product (**4a**) was obtained with a good conversion, but only with a

Table 1: Optimization of the diastereoselectivity.



Entry	Catalyst	Ligand	d.r.[a]
1	CuCN·2LiCl[b]	–	68:32
2	$PdCl_2$	tmpp	95:5 (4)
3	$PdCl_2$	 **6a**: R = H **6b**: R = Me	96:4 (<3) 98:2 (<2)
4	$PdCl_2$	 **7a**: R = H **7b**: R = Me **7c**: R = Ph **7d**: R = *t*Bu	96:4 (<3) 98:2 (<2) 96:4 (<4) 96:4 (<3)
5	$[PdCl_2(PhCN)_2]$	**7b**	96:4 (3)
6	$[Pd(dba)_2]$	**7b**	97:3 (2)
7	$[Ni(acac)_2]$	**7b**	87:13

[a] Determined by GC analysis on a capillary column. The percentage of regioisomers is given in parentheses. [b] 10 mol%.

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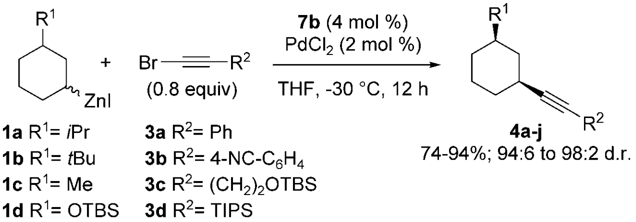
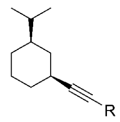
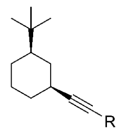
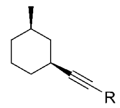
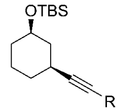
modest diastereoselectivity (68:32 d.r.; Table 1, entry 1). On switching to palladium catalysts, we found that the complex $[PdCl_2(tmpp)_2]$ (tmpp = tris(2,4,6-trimethoxyphenyl)phosphine)[15] provided **4a** with a high d.r. of 95:5. We also observed the formation of some regioisomeric product (ca. 4 %).[16] This diastereoselectivity could be further improved by replacing the phosphine ligand tmpp with various bipyridines (**6a**,**b**; entry 3) and orthophenanthrolines (**7a**–**d**; entry 4). The N ligands clearly proved to be superior. The commercially available and inexpensive neocuproine[17] (**7b**) combined excellent diastereoselectivity with the low formation of regioisomers (< 2 %). $PdCl_2$ was found to be the best Pd source and switching from Pd to Ni as the catalyst resulted in a deterioration of the d.r. (87:13 d.r.; entry 7). Bidentate N ligands are known to stabilize Pd^0 more efficiently than monodentate phosphines,[17b] thus leading to a faster reductive elimination and minimizing unwanted β-hydride elimination and the formation of regioisomeric products.

The 3-substituted cyclohexylzinc reagent **1a** was subsequently subjected to cross-coupling reactions with a range of 1-bromoalkynes **3a**–**d** in the presence of the optimized catalyst system (2 mol % $PdCl_2$, 4 mol % **7b**). The expected thermodynamically preferred *cis*-1,3-disubstituted cyclohexane derivatives[18] were obtained with good yields and excellent diastereoselectivities (94:6 to 98:2 d.r.; Table 2, entries 1–5). Bromoalkynes bearing aromatic (**3a**,**b**), aliphatic (**3c**), and silyl moieties (**3d**) were successfully coupled. Increasing the steric bulk of the substituent from *i*Pr to *t*Bu on the cyclohexylzinc reagent did not have an effect on the diastereoselectivity or yield (compare **4c** (77 %; 97:3 d.r.) and **4f** (74 %; 97:3 d.r.); entries 3 and 6). Replacing the relatively large *i*Pr group with the sterically much less demanding methyl group only led to a slight loss of diastereoselectivity (compare **4a** (82 %; 98:2 d.r.) with **4g** (79 %; 96:4 d.r.); entries 1 and 7). Functionalized cyclohexylzinc reagents bearing an OTBS ($OSiMe_2tBu$) functionality underwent the palladium-catalyzed cross-coupling reactions with equally high diastereoselectivities (96:4 to 98:2 d.r.; **4i**,**j**; entries 9 and 10).

Next, we performed $C(sp^3)-C(sp)$ coupling reactions with the 4-substituted cyclohexylzinc reagents **2a**–**c** (Table 2). To our delight, the diastereoselectivity was as high as those obtained for the coupling reactions of the 3-substituted cyclohexylzinc iodides (94:6 to 98:2 d.r.; compare Tables 2 and 3), showing an excellent remote stereocontrol. In all cases, the thermodynamically favored *trans*-1,4-disubstituted cyclohexanes were preferentially formed (Table 3).[18] As for the 3-substituted cyclohexylzinc reagents, the size of the respective substituents only had a minor effect on the diastereoselectivity. Thus, cyclohexylzinc reagent **2a** bearing a bulky *t*Bu group furnished the coupling products **5a**–**d** with ≥ 96:4 d.r. (Table 3, entries 1–4), while the coupling reactions of the methyl-substituted zinc reagent **2b** resulted in a slightly lower d.r. of 95:5 (entries 5 and 6). Cross-coupling reactions of the functionalized organozinc iodide **2c** also proceeded highly diastereoselectively (95:5 to 96:4 d.r.) to provide the *trans*-configured products **5g**–**i** in excellent yields (88–94 %; entries 7–9).

Table 2: Diastereoselective $C(sp^3)-C(sp)$ coupling of 3-substituted cyclohexylzinc reagents.



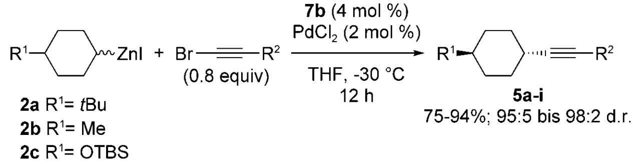
Entry		Product	Yield [%][a]	d.r.[b]
1 2 3 4		**4a**: R = Ph **4b**: R = 4-NC-C_6H_4 **4c**: R = $(CH_2)_2OTBS$ **4d**: R = TIPS	82 87 77 79	98:2 94:6 97:3 94:6
			76[c]	96:4[c]
5 6		**4e**: R = 4-NC-C_6H_4 **4f**: R = $(CH_2)_2OTBS$	85 74	95:5 97:3
7 8		**4g**: R = Ph **4h**: R = 4-NC-C_6H_4	79 88	96:4 96:4
9 10		**4i**: R = TIPS **4j**: Ar = $(CH_2)_2OTBS$	81 94	98:2 96:4

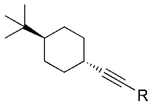
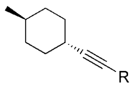
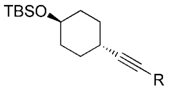
[a] Yield of the isolated analytically pure product. [b] Determined by GC analysis on a capillary column before and after purification. The percentage of regioisomers produced as by-products was between 0–5 %. See the Supporting Information for details. [c] **6b** (4 mol %) was used. TIPS = triisopropylsilyl.

Steric interactions between the ligand on the palladium center and the substituent on the cyclohexyl ring dictate the stereochemical outcome of these diastereoselective cross-coupling reactions. The stereocontrol is assumed to be effected by a selective transmetalation step between the respective cyclohexylzinc reagents and the alkynyl(bromo)palladium complex, which leads to the formation of the thermodynamically most stable palladium intermediates. Subsequent reductive elimination proceeds with retention of configuration and furnishes the corresponding 1,3- and 1,4-disubstituted products with high diastereoselectivity.[11]

trans-1,4-Disubstituted cyclohexanes,[19] including their alkynyl-substituted derivatives,[20] constitute important building blocks for liquid crystals because of their unique properties, such as low viscosity coefficients and higher optical anisotropy. Our new coupling procedure offers a direct and highly stereoselective route to such compounds (Table 3). Supramolecular chirality can be induced in liquid crystals by the use of chiral dopants.[21] Since menthyl-capped dopants[22] have already been applied successfully to amplify chirality in liquid crystals, we envisioned the synthesis of **8**, which may

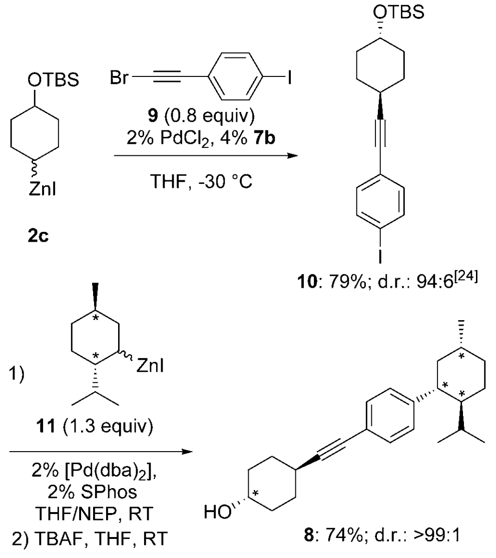
Table 3: Diastereoselective C(sp^3)−C(sp) coupling of 4-substituted cyclohexylzinc reagents.



Entry	Product		Yield [%][a]	d.r.[b]
1		**5a**: R = Ph	76	97:3
2		**5b**: R = 4-NC-C$_6$H$_4$	84	96:4
3		**5c**: R = (CH$_2$)$_2$OTBS	79	98:2
4		**5d**: R = TIPS	75	96:4
5		**5e**: R = (CH$_2$)$_2$OTBS	74	95:5
6		**5f**: R = TIPS	71	95:5
7		**5g**: R = (CH$_2$)$_2$OTBS	88	96:4
8		**5h**: R = TIPS	93	95:5
9		**5i**: R = 4-NC-C$_6$H$_4$	94	96:4

[a] Yield of isolated analytically pure product. [b] Determined by GC analysis on a capillary column before and after purification. The percentage of regioisomers produced as by-products was between 1–6%. See the Supporting Information for details.

serve as a building block for chiral dopants because of its structural similarity to some 1,4-disubstituted cyclohexyl-based mesogens.[20] Thus, the functionalized cyclohexylzinc reagent **2c** was subjected to cross-coupling with the bromoalkyne **9** to furnish the *trans*-1,4-cyclohexylalkyne **10** (79%, 94:6 d.r.; Scheme 2). The aromatic iodo substituent of **10** allowed a further cross-coupling with (−)-menthylzinc iodide (**11**) by using [Pd(dba)$_2$] and SPhos (dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine)[23] as the catalyst system.[11] Deprotection with TBAF furnished the rod-shaped, chiral product **8** with complete diastereoselectivity (74%; > 99:1 d.r.).



Scheme 2. Sequential diastereoselective C(sp^3)−C(sp) and C(sp^3)−C(sp^2) coupling leading to **8**, a potential building block for chiral dopants. dba = *trans,trans*-dibenzylideneacetone, NEP = *N*-ethylpyrrolidone, TBAF = tetrabutylammonium fluoride.

In summary, we have developed a general and highly diastereoselective method for the palladium-catalyzed cross-coupling of 3- and 4-substituted cyclohexylzinc reagents. Remarkably, the cyclohexyl substituents remote from the carbon–zinc bond induce very high diastereoselectivity. The coupling of the 4-substituted cyclohexylzinc reagents is of special interest as it offers a straightforward and highly stereoselective access to possible liquid crystalline mesogens.[20] Sequential combination of diastereoselective C(sp^3)−C(sp) and C(sp^3)−C(sp^2) coupling was shown to be applicable to the construction of building blocks of potential chiral dopants. Further extensions of this method for its direct application to the synthesis of liquid crystals are currently being investigated in our laboratories.

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Keywords: alkynes · C−C coupling · diastereoselectivity · homogeneous catalysis · palladium

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[24] The diastereomeric ratio of 94:6 represents the diastereoselectivity of the crude reaction mixture. The minor diastereomer (6%) could be removed through purification by column chromatography.