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Cobalt-Catalyzed Diastereoselective Cross-Couplings between Alkynylzinc Pivalates and Functionalized Cyclic Iodides or Bromides

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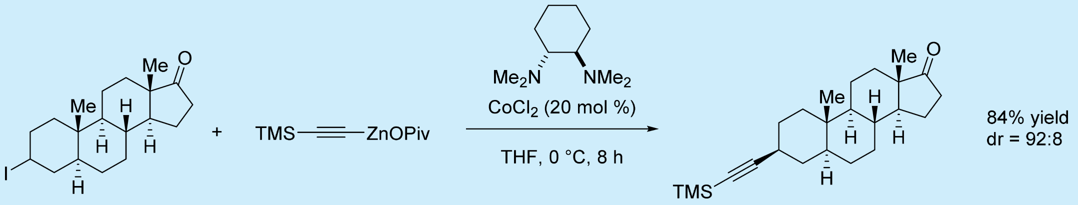
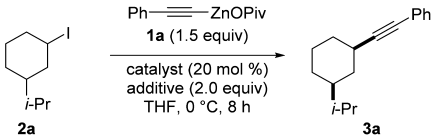
Supporting Information



ABSTRACT: Various 1,2-, 1,3-, and 1,4-substituted cyclic iodides or bromides undergo highly diastereoselective cross-couplings (diastereoselectivity (dr) up to 99:1) with a range of alkynylzinc pivalates, using $CoCl_2$ (20 mol %) and *trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine as a catalytic system.

Transition-metal-catalyzed diastereoselective cross-couplings represent an excellent way for the stereoselective synthesis of organic molecules.[1] Although palladium has been employed for such stereoselective cross-couplings,[2] the use of alternative, less-expensive, and less-toxic metals, such as iron[3] or cobalt,[4] has recently attracted a lot of attention. In most cross-coupling reactions, organomagnesium reagents, including alkynylmagnesium halides, are the preferred nucleophiles.[2e,3e,4g,h,5] Recently, we have shown that the use of organozinc reagents can be advantageous for such cross-couplings, because of the high tolerance of functional groups of these organometallics.[6] Particularly, the use of organozinc pivalates of the type RZnOPiv·MgX_2[7] enables fast and efficient cobalt-catalyzed cross-couplings.[8] We have also reported that alkynylzinc pivalates are readily prepared from the corresponding alkynes. After solvent evaporation, solid organozinc pivalates are obtained with enhanced air and moisture stability.[9] Also, these organozinc pivalates undergo convenient cobalt-catalyzed cross-couplings with aryl halides and heteroaryl halides.[10] Herein, we report a new, diastereoselective cross-coupling between alkynylzinc pivalates of type **1** and various functionalized cyclic iodides or bromides of type **2**. In preliminary experiments, 3-isopropylcyclohexyl iodide (**2a**) was treated with 2-phenylethynylzinc pivalate (**1a**) at 0 °C under various conditions (Table 1). First, we tested some low-cost transition-metal salts. $NiCl_2$,[5c,11] $MnCl_2$,[12] $FeCl_2$,[3e,5a,b] and $CuCl_2$,[13] without any additive or in the presence of TMEDA (*N,N,N′,N′*-tetramethylethylenediamine), were unsuitable metal catalysts for this coupling (entries 1−4 in Table 1). However, using 20 mol % of $CoCl_2$ and TMEDA as an additive provided **3a** in 67% yield, but with moderate diastereoselectivity (dr = 85:15, entry 6 in Table 1).

Table 1. Optimization of the Conditions for the Diastereoselective Cross-Coupling of 1,3-Disubstituted Cyclohexyl Iodide (2a) with Alkynylzinc Pivalate (1a)



2a **3a**

entry	catalyst	additive	yield[a] (%)	dr[a]
1	$NiCl_2$		0 (0)[b]	n.d. (n.d.)[b]
2	$MnCl_2$		0 (0)[b]	n.d. (n.d.)[b]
3	$FeCl_2$		0 (0)[b]	n.d. (n.d.)[b]
4	$CuCl_2$		0 (0)[b]	n.d. (n.d.)[b]
5	$CoCl_2$		5	80:20
6	$CoCl_2$	TMEDA	67	85:15
7	$CoBr_2$	TMEDA	11	85:15
8	$CoCl_2$·2LiCl	TMEDA	62	85:15
9	$CoCl_2$	**L1**	2	n.d.
10	$CoCl_2$	**L2**	38	88:12
11	$CoCl_2$	**L3**	86 (78)[c]	92:8
12	$CoCl_2$[d]	**L3**	85	92:8

[a] As determined by GC analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. Only the major diastereomer is shown. [b] 2.0 equiv of TMEDA were used. [c] Isolated yield. [d] $CoCl_2$ (99.99% purity).

Other cobalt sources, such as $CoBr_2$ or $CoCl_2$·2LiCl, did not have beneficial effects (see entries 7 and 8 in Table 1). The diastereoselectivity was improved by screening various *N*-ligands (entries 9−11 in Table 1). Clearly, *trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine (**L3**) gave the best results (entry 11 in Table 1). Also, varying the solvent system did not improve the reaction outcome.[14] At this point, we verified that

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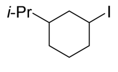
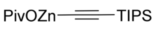
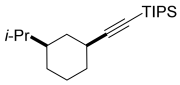
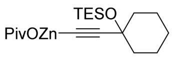
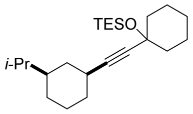
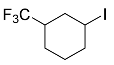
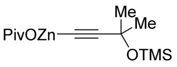
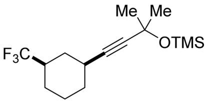
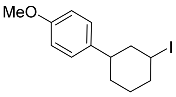
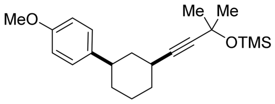
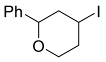
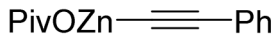
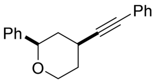
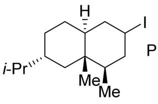
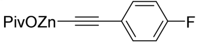
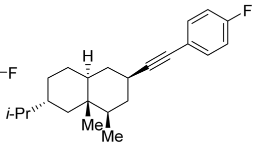
no other metal contaminations are responsible for this catalysis. Thus, using $CoCl_2$ (99.99% purity) led to **3a** in 85% yield (dr = 92:8, entry 12 in Table 1). With these optimized reaction conditions in hand, we performed a range of coupling reactions of various alkynylzinc pivalates of type **1** with 1,3-substituted cyclic alkyl iodides of type **2**, furnishing the thermodynamically favored *cis*-isomer (see Table 2).[15]

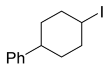
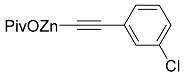
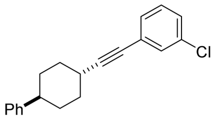
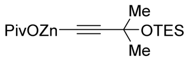
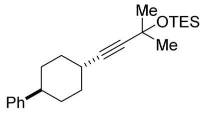
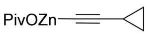
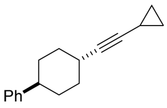
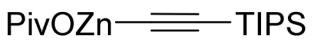
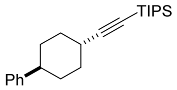
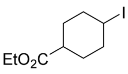
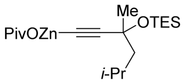
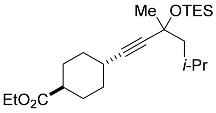
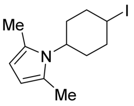
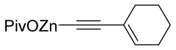
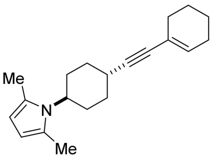
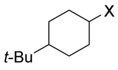
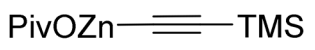
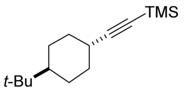
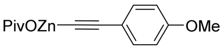
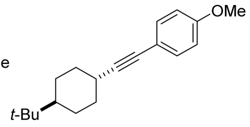
Table 2. Products (3) Obtained by the Diastereoselective Cross-Coupling of 1,3-Disubstituted Cyclohexyl Iodides (2) with Various Alkynylzinc Pivalates (1)

entry	electrophile (**2**)	zinc reagent (**1**)	product[a] (**3**)
1	 **2a**[b]	 **1b**	 **3b**: 95% (dr = 95:5)
2	**2a**[b]	 **1c**	 **3c**: 91% (dr = 98:2)
3	 **2b**[b]	 **1d**	 **3d**: 62% (dr = 90:10)
4	 **2c**[b]	**1d**	 **3e**: 78% (dr = 98:2)
5	 **2d**[b]	 **1a**	 **3f**: 76% (dr = 93:7)
6	 **2e**[c]	 **1e**	 **3g**: 60% (dr = 94:6)

[a] Isolated yield. The diastereoselectivity (dr) was determined by GC analysis. The major diastereomer is shown. [b] dr = 99:1. [c] dr = 85:15.

The coupling of **2a** with bulky alkynes, such as zinc pivalates **1b** or **1c**, resulted in the corresponding coupling products (**3b** or **3c**) in 91%−95% yield and high diastereoselectivity (dr = 95:5−98:2, entries 1 and 2 in Table 2). Also, the propargylic alcohol derivative **1d** was successfully coupled with cyclic iodides bearing a trifluoromethyl **2b** and an aryl group **2c**, to provide **3d** and **3e** in 62%−78% yield, respectively, with a dr up to 98:2 (entries 3 and 4 in Table 2). Pyran **3f** was obtained by coupling of the heterocyclic iodide **2d** with **1a** in 76% yield and dr = 93:7 (entry 5 in Table 2). Remarkably, the cross-coupling of iodide **2e**, derived from the natural product (+)-nootkatone,[16] proceeded smoothly with alkynylzinc pivalate **1e**, leading to the coupling product **3g** in 60% yield (dr = 96:4, entry 6 in Table 2). In addition, this cobalt-catalyzed cross-coupling was applied to 1,4-disubstituted cyclohexyl halides, leading to *trans*-coupling products (see Table 3).[17] Thus, 4-phenyl cyclohexyl iodide (**2f**) reacted smoothly with various alkynylzinc pivalates (**1b**, **1f**, **1g**, **1h**), resulting in the products **3h**−**3k** in 68%−96% yield (dr = 90:10−99:1, entries 1−4 in Table 3). Also, an ester function was tolerated in these couplings, and the iodoester **2g** was converted to the *trans*-alkyne **3l** in 71% yield (dr = 90:10, entry 5 in Table 3).

Table 3. Products (3) Obtained by the Diastereoselective Cross-Coupling of 1,4-Disubstituted Cyclohexyl Halides (2) with Various Alkynylzinc Pivalates (1)

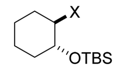
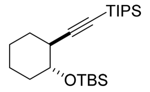
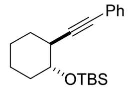
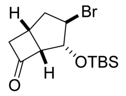
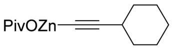
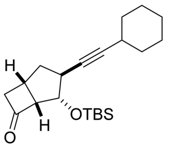
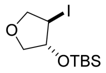
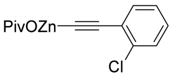
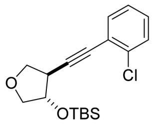
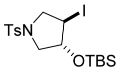
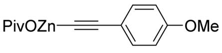
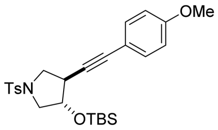
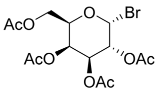
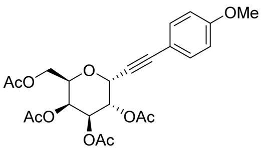
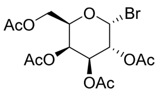
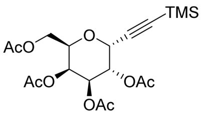
entry	electrophile (**2**)	zinc reagent (**1**)	product[a] (**3**)
1	 **2f**[b]	 **1f**	 **3h**: 68% (dr = 90:10)
2	**2f**[b]	 **1g**	 **3i**: 95% (dr = 99:1)
3	**2f**[b]	 **1h**	 **3j**: 71% (dr = 95:5)
4	**2f**[b]	 **1b**	 **3k**: 96% (dr = 98:2)
5	 **2g**[c]	 **1i**	 **3l**: 71% (dr = 90:10)
6	 **2h**[d]	 **1j**	 **3m**: 83% (dr = 95:5)
7	 **2i**: X = Br[e]	 **1k**	 **3n**: 71% (dr = 90:10)
8	**2j**: X = I[e]		**3n**: 84% (dr = 90:10)
9	**2j** X = I[e]	 **1l**	 **3o**: 73% (dr = 94:6)

[a] Isolated yield. The diastereoselectivity (dr) was determined by GC-analysis. The major diastereomer is shown. [b] dr = 92:8. [c] dr = 68:32. [d] dr = 90:10. [e] dr = 99:1.

Furthermore, pyrrole derivative **2h** was coupled with **1j**, furnishing the *trans*-pyrrole-substituted cyclohexane derivative **3m** in 83% yield and a dr of 95:5 (entry 6 in Table 3). 4-(*tert*-Butyl)cyclohexyl bromide (**2i**) reacts readily with the silylated alkynylzinc pivalate **1k**, leading to the *trans*-1,4-cyclohexane derivative **3n** (71%, dr = 90:10, entry 7 in Table 3). Also, the corresponding cyclohexyl iodide **2j** undergoes such couplings with alkynylzinc pivalates **1k** and **1l**, providing the products **3n** and **3o** in 73%−84% yields and a dr up to 94:6 (entries 8 and 9 in Table 3).

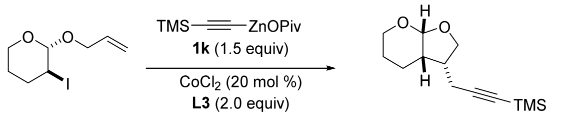
In addition, this cross-coupling was performed with 1,2-substituted cyclic halides and bromo-glycosides (see Table 4).[3f,4e] TBS-protected iodo or bromohydrins **2k** and **2l** were successfully coupled with alkynylzinc pivalate **1b**, leading to the thermodynamically preferred *trans*-substituted product **3p** in 60%−78% yield (dr = 99:1, entry 1 in Table 4).[18] Similarly, iodohydrin **2k** reacted with **1a** to give the *trans*-1,2-disubstituted cyclohexane derivative **3q** in 72% yield (dr = 94:6, entry 3 in Table 4). Bicyclic bromide **2m** was converted to the alkynylated product **3r** in 62% yield (dr = 99:1, entry 4 in Table 4). This cobalt-catalyzed cross-coupling was further extended to five-membered heterocyclic halohydrins **2n** and **2o** (entries 5 and 6 in Table 4). The coupling of the TBS-protected cyclic iodohydrin **2n** with alkynylzinc pivalate **1n** affords the desired substituted tetrahydrofuran **3s** in 63% yield (dr = 99:1, entry 5 in Table 4). Coupling of the iodopyrrolidine derivative **2o** with **1l** affords the *trans*-1,2-disubstituted heterocycle **3t** in 75% yield and high diastereoselectivity (dr = 99:1, entry 6 in Table 4). Remarkably, this diastereoselective cross-coupling could also be performed using the bromo-glycoside **2p**. Thus, galactose derivative **2p** was successfully cross-coupled under cobalt catalysis with alkynylzinc pivalates **1k** and **1l**, furnishing the α-C-glycosides **3u** and **3v** in 52%−54% yields and high α/β-selectivity (α/β = 94:6−95:5, entries 7 and 8 in Table 4). The stereochemical outcome of these cobalt-catalyzed cross-couplings with bromo-glycosides could be explained with the formation of an anomeric α-radical intermediate.[3e,f,4a,e,19] The reaction between the allyl-protected iodohydrin **2q** and the alkynylzinc pivalate **1k** led to the bicyclic product **3w** in 68% yield (dr = 95:5; see Scheme 1).[20] This result confirms a radical pathway for this cross-coupling.

Table 4. Products (3) Obtained by the Diastereoselective Cross-Coupling of 1,2-Disubstituted Cyclic (Hetero)alkyl Halides (2) with Alkynylzinc Pivalates (1)

entry	electrophile (**2**)	zinc reagent (**1**)	product[a] (**3**)
		PivOZn−≡−TIPS	
1	**2k**: X = I[b]	**1b**	**3p**: X = I: 77%[c] (dr = 99:1)
2	**2l**: X = Br[b]		**3p**: X = Br: 60% (dr = 99:1)
		PivOZn−≡−Ph	
3	**2k**[b]	**1a**	**3q**: 72% (dr = 96:4)
			
4	**2m**[b]	**1m**	**3r**: 62% (dr = 99:1)
			
5	**2n**[b]	**1n**	**3s**:63% (dr = 99:1)
			
6	**2o**[b]	**1l**	**3t**: 75% (dr = 99:1)
			
7	**2p**[b]	**1l**	**3u**: 54% (dr = 94:6)
		PivOZn−≡−TMS	
8	**2p**[b]	**1k**	**3v**: 52% (dr = 95:5)

[a] Isolated yield. The diastereoselectivity (dr) was determined by GC-analysis. The major diastereomer is shown. [b] dr = 99:1. [c] 5 mmol scale.

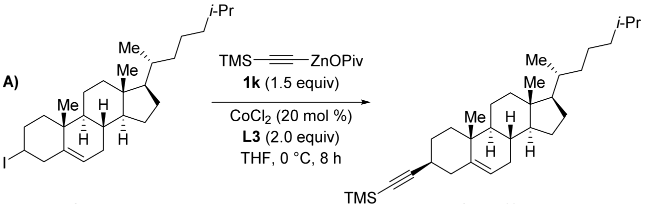
Scheme 1. Diastereoselective Cyclization of Iodide 2q with Alkynylzinc Pivalate 1k



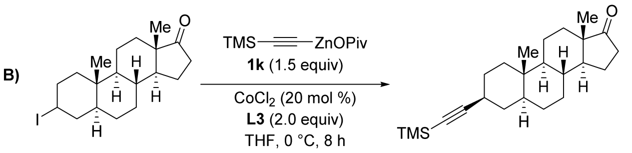
2q (dr = 99:1) **3w**: 68% yield (dr = 95:5)

Finally, silylated alkynylzinc reagent **1k** was coupled with various steroid derivatives (Scheme 2). Using cholesteryl iodide (**2r**) led to the alkynylated steroid **3x** in 75% yield (dr = 98:2).[21] Remarkably, the use of an iodo epiandrosterone derivative containing a ketone moiety also proceeded smoothly in 84% yield (dr = 92:2).

Scheme 2. Diastereoselective Cross-Coupling of Steroid Derivatives 2r and 2s with Alkynylzinc Pivalate 1k



2r (dr = 98:2) **3x**: 75% yield (dr = 98:2)



2s (dr = 95:5) **3y**: 84% yield (dr = 92:8)

In conclusion, we have shown that a cobalt-catalyzed cross-coupling reactions of 1,2- 1,3-, and 1,4-substituted 5- and 6-membered cyclic (hetero)alkyl halides with alkynylzinc pivalates proceed with high and predictable diastereoselectivity. Also, alkynyl-substituted glycosides were prepared with excellent α-selectivity. Further mechanistic studies and applications to more functionalized ring systems and heterocycles are currently underway in our laboratories.

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■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00784.

Full experimental details and ^{1}H NMR and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1826096 and 1826097 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) The stereochemistry of **3a** and **3b** was confirmed by literature NMR data. See: Thaler, T.; Guo, L.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 2174.

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(20) The stereochemistry of **3w** was determined by NOESY-NMR spectroscopy.

(21) The stereochemistry of **3x** was determined by crystal structure analysis.