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Regioselective Transition-Metal-Free Allyl–Allyl Cross-Couplings

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Abstract: Readily prepared allylic zinc halides undergo S_N^2 type substitutions with allylic bromides in a 1:1 mixture of THF and DMPU providing 1,5-dienes regioselectively. The allylic zinc species reacts at the most branched end (γ -position) of the allylic system furnishing exclusively γ , α' -allyl-allyl crosscoupling products. Remarkably, the double bond stereochemistry of the allylic halide is maintained during the crosscoupling process. Also several functional groups (ester, nitrile) are tolerated. This cross-coupling of allylic zinc reagents can be extended to propargylic and benzylic halides. DFT calculations show the importance of lithium chloride in this substitution.

ransition-metal-catalyzed cross-couplings represent a major tool for forming new carbon-carbon bonds.[1] Although Pd-^[2] and Ni-^[3] catalyzed cross-couplings have found numerous applications, the search for alternative transition-metal catalysts such as Fe and Co salts^[4] have become increasingly important owing to economical and toxicity issues. Alternatively, the performance of crosscouplings without transition metals as reported by Hayashi,^[5] Uchiyama,^[6] and others^[7] opens new perspectives for sustainable C-C bond formations. In this respect, allylic organometallics represent a promising class of organometallic reagents since the carbon-metal bond in these compounds is typically highly polarized and therefore highly reactive. Thus, the cross-coupling between 3-substituted allylic organometallics of type 1 with 3-substituted allylic halides of type 2 may provide up to four regioisomeric coupling products of type 3 (Scheme 1).

In pioneering work, Y. Yamamoto and co-workers achieved a regioselective head-to-tail (γ, α') cross-coupling using allylic boronate complexes and allylic halides.^[8] More



Scheme 1. Cross-coupling of allylic organometallic **1** with allylic halide **2** leading to four regioisomeric coupling products of type **3**.

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recently, several transition-metal-catalyzed allyl–allyl crosscouplings have been reported by the groups of Morken^[9] and others.^[10] H. Yamamoto and co-workers have shown that both α - and γ -selective allyl–allyl cross-couplings can be accomplished using either allylic barium halides^[11] or allylic magnesium halides.^[12]

Recently, we have described convenient mild preparations of functionalized allylic zinc reagents and demonstrated their utility in synthesis.^[13] In contrast to most reactive allylic organometallics, these allylic zinc reagents tolerate various functional groups. Therefore, we envisioned that the allyl– allyl cross-coupling between such functionalized allylic zinc reagents and substituted allylic halides may provide access to a broad range of functionalized 1,5-dienes of type **3**. Herein, we report a highly regioselective head-to-tail cross-coupling leading to products of type γ, α' -**3** and tolerating sensitive functional groups such as esters and nitriles.

In preliminary experiments, we examined the crosscoupling of prenylzinc bromide (1a), which was generated by the insertion of zinc dust in the presence of LiCl in THF (1 h, 25 °C, 72 % yield), with (*E*)-1-bromonon-2-ene (2a), at various temperatures and in several solvent mixtures (Table 1). Thus, the addition of the zinc species 1a to the allylic bromide 2a in THF at room temperature led to a mixture of all four regioisomers ($\alpha, \alpha'/\alpha, \gamma'/\gamma, \alpha'/\gamma, \gamma' =$ 33:25:35:7; entry 1). Selectivity in favor of the α, α' -isomer was obtained by lowering the reaction temperature to -10 °C and -40 °C (57% and 88% of the α, α' -isomer were obtained, respectively; entries 2 and 3). This α, α' -regioselectivity was not further improved as we found that the addition of various cosolvents leads to a shift to the regioisomer $\gamma, \alpha'-3a$.

 Table 1: Optimization of the conditions for the allyl-allyl cross-coupling.

Me Me nHex	α ZnBr + 1a ^[a] - 25 α ' 2a	THF b°C, 2 h nHex α, α' -	Me. +	Me + nHe α,γ'-3a	x γ,c	// лНех х'-За	+ Μe
Entry	7 [°C]	$Cosolvent^{[b]}$	α,α΄	α,γ΄	γ,α΄	γ,γ΄	Yield ^[c] [%]
1	25	none	33	25	35	7	75
2	-10	none	57	27	10	6	65
3	-40	none	88	8	4	0	61
4	25	toluene	4	5	89	2	94
5	25	<i>n</i> -hexane	16	2	82	0	82
6	25	1,4-dioxane	5	10	81	4	92
7	25	DMSO	0	5	91	4	100
8	25	NMP	0	5	95	0	100
9	25	DMPU	0	0	100	0	100 (91) ^[d]
10	25	DMPU ^[e]	10	15	71	4	100

[a] LiCl is omitted for clarity. [b] A 1:1 mixture with THF was used.
[c] Determined by GC analysis using undecane as an internal standard.
[d] Yield of isolated product. [e] DMPU was just used as an additive (3.0 equiv with respect to the organozinc reagent).

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Thus, the use of a 1:1 mixture of THF and unpolar solvents such as toluene (entry 4) and *n*-hexane (entry 5) furnished selectively the cross-coupling product (γ , α' -**3a**) in 89% and 82% selectivity, respectively. Switching the solvent to a 1:1 mixture of 1,4-dioxane and THF led to a similar result (81% of γ , α -**3a**) with an overall yield of 92% (entry 6). Interestingly, significant regioselectivity improvements were achieved by using DMSO, NMP, and DMPU as cosolvents (up to 100% γ , α' -selectivity; entries 7–9), allowing us to isolate the pure coupling product (γ , α' -**3a**) in 91% yield (entry 9 and Scheme 2). Lowering the amount of DMPU to just 3 equiv-



Scheme 2. Transition-metal-free allyl-allyl cross-coupling leading to γ , α' -products of type **3** after 3 h at room temperature with very high selectivity (values in parentheses represent the γ , α'/α , α'/α , α'/γ , γ' ratio). [a] LiCl is omitted for clarity. Yield determined by titration with I_2 .

alents led only to a decrease in selectivity (entry 10). Furthermore, by inverting the polarity of the reagents, we were also able to prepare selectively the α, γ' -regioisomer $(\alpha, \gamma' - 3a)$. Thus, instead of using prenylzinc bromide (1a), we have used directly prenyl bromide (2b) and have replaced the allylic bromide (2a) with the corresponding zinc reagent (1b). Now, the cross-coupling between **2b** and **1b** produced only the regioisomer α, γ' -**3a** with 97% selectivity and 78% yield (Scheme 2). This γ, α' -selectivity was general and the sterically hindered prenylzinc bromide (1a) reacts smoothly with the allylic bromides 2c and 2d producing the coupling products **3b** and **3c** in 82–91% yield (Table 2, entries 1 and 2).^[14] (*E*)-Non-2-en-1-ylzinc bromide (1b) and cinnamylzinc chloride (1c) display a similar behavior leading to 3d,e in 92–96% yield after 3 h (entries 3 and 4). In addition, geranylzinc bromide (1d) and nerylzinc bromide (1e) react with the functionalized allylic bromides 2e and 2c furnishing the branched isomers 3f and 3g in 90-92% yield (entries 5 and 6).

Remarkably, the substituted allylzinc compounds $\mathbf{1}\mathbf{f}^{[15]}$ and $\mathbf{1g}^{[16]}$ react smoothly with the allylic bromide $\mathbf{2}\mathbf{f}$ and prenyl bromide (**2b**) leading to the polyfunctionalized products (**3h**,**i**) in 83–90% yield (entries 7 and 8). Similarly, the allylic zinc reagents **1a** and **1d** were converted into the corresponding products (γ , α' -**3j** and γ , α' -**3k**) in 79–83% yield (entries 9 and 10). Finally, the allylzinc reagent **1h** reacts twice with (*E*)-1,4-dibromobut-2-ene (**2h**) furnishing the symmetrical product (*E*)-**3l** as the only isomer (*E*/*Z* > 99:1) in 90% yield after 3 h (entry 11).

Remarkably, these cross-couplings proceed with retention of the double bond configuration of the allylic bromide

Table 2: Allyl-allyl cross-couplings in a 1:1 mixture of THF and DMPU after 1–3 h at 25 °C.

Entry	Zinc reagent ^[a]	Electrophile ^[b]	Product ^[c]
	Me Me	CO ₂ tBu	CO ₂ tBu Me Me
1	l a Me Me	2c CN Br	3b: 82%
2	la	2 d	3c: 91%
	<i>n</i> Hex ZnBr	CO ₂ tBu	//Hex
3	1 b (25, 2 h, 77)	2c	3 d: 92%
	PhZnCl	CO ₂ tBu	Ph
4	1c (25, 2 h, 86)	2c	3e: 96%
	ZnBr	CO ₂ Et	Me Me CO ₂ Et
5	1 d (25, 1 h, 83)	2e	3 f : 92%
	ZnBr	CO ₂ tBu	Me Me CO ₂ fBu
6	1e (25, 1 h, 58) OBn ZnCl	2c CO ₂ Et Br	3 g : 90% CO ₂ Et
7	1 f (50, 8 h, 41) CO ₂ Et ZnCl	2 f Me Me Br	3 h : 90% CO ₂ Et Me
8	1g (25, 1 h, 60) Me	2b TMSBr	3i: 83 % Me Me
9	Me CnBr	2g	3j: 79%
	Me	Me	Me Me Me
	ZnBr Me	Me	Me
10	1 d	2 b	3 k∶ 83 % ^[d] Me
	Me ZnBr	Br	Me
11	1 h ^[e] (25, 1 h, 66)	2 h	3 1: 90%

[a] LiCl is omitted for clarity. In parentheses: temperature, time, yield [%] for the insertion. Yields determined by titration with I₂. [b] 0.8 equiv of electrophile was used. [c] Yields refer to isolated, analytically pure products. [d] 6% of the α, α' -isomer was formed. [e] 2.4 equiv of organozinc was used.

indicating an S_N2-type substitution. Thus, the zinc reagents **1i** and **1b** react with geranyl bromide (**2i**) selectively to give the corresponding (*E*)-1,5,9-trienes (**3m**,**n**) in 74–84% yield (Scheme 3). In a control experiment, prenylzinc bromides (**1a**) was treated with the (*E*)- and (*Z*)-allylic bromides **2j**,**k** providing stereoselectively the expected γ , α' -regioisomers (*E*)- γ , α' -**30** and (*Z*)- γ , α' -**30** in 76–77% yield and >99% retention of the double bond configuration (Scheme 3).

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Scheme 3. Allyl-allyl cross-coupling leading to γ , α' -products of type **3** with full retention of the double bond configuration. [a] LiCl is omitted for clarity.

This cross-coupling was also applicable to benzylic and propargylic halides. Thus, the reaction of prenylzinc bromide (1a) and (E)-non-2-en-1-ylzinc bromide (1b) with propargylic halides of type 4 produces 1,5-enynes of type 5 (Scheme 4). Accordingly, the cross-coupling of 1b with the propargylic chloride 4a provides only the 1,5-enyne 5a in 88% yield.



Scheme 4. Cross-coupling of allylic zinc reagents of type 1 with propargylic and benzylic halides leading to γ , α' -products of type 5 and 7. [a] LiCl is omitted for clarity. [b] 0.80 equiv of electrophile were used. [c] Yields refer to isolated, analytically pure products. [d] The propargylic chloride was used instead of the bromide. [e] 0.40 equiv of electrophile was used.

The reaction of prenylzinc bromide (1a) with 7-bromohept-5-ynoate (4b) furnishes the corresponding functionalized 1,5-enyne 5b in 79% yield. Furthermore, the coupling of zinc reagent 1a with 1,4-dibromobut-2-yne (4c) selectively affords the symmetrical product 5c in 85% yield. Interestingly, benzyl bromides (6a,b) reacted under our standard reaction conditions furnishing the substitution products 7a and 7b in 63–72% yield. However, prenylzinc bromide did not react with 1-bromononane. In addition, in a control experiment, prenylzinc bromide (1a) was added to a 1:1 mixture of 1-bromononane and (*E*)-1-bromonon-2-ene (2a) which led to the allyl-allyl cross-coupling product γ, α' -3a exclusively.

In order to support the experimental outcome of this selective transformation the reaction pathway was investigated using double hybrid density functional theory (DFT).^[17] The addition of LiCl is currently believed to accelerate reactions of organometallic reagents through increased formation of monomeric species or ate-like complexes.^[18] In line with this rationalization we find that hetero dimers of type 8 represent the most stable structures in solution; this is indicated by the significant exergonicity of the exchange reaction of $(LiCl)_2(sol)_4$ with $(RZnBr)_2(sol)_2$ $(\Delta G_{sol}(THF) =$ $-14.4 \text{ kJ mol}^{-1}$, $\Delta G_{sol}(\text{DMPU}) = -27.1 \text{ kJ mol}^{-1}$) at the B2PLYP-D3(FC)/def2-TZVPP level^[19] including implicit SMD/B3LYP/6-31G(d) solvation.^[20] Indeed, ¹H and ¹³C NMR shifts in THF obtained during the LiCl-mediated oxidative addition of zinc to the carbon-bromine bond of prenvl bromide (2b) correlate quite well with theoretically calculated chemical shifts of lithium zinc dimer 8-THF at the mPW1K/IGLO-III level of theory^[21] (see the Supporting Information). Substituted allylic organometallics often show high diastereoselectivity in reactions with electrophiles due to their rather ordered cyclic or acyclic transition states.^[22] How LiCl facilitates the construction of highly ordered but unstrained transition states in substitution reactions with prenyl zinc nucleophiles is shown in an exemplary fashion in Figure 1 for the formation of γ, α' -cross-coupling products of type 3. Starting from mixed aggregate 8-THF, the reaction is here assumed to involve initial exchange of THF by DMPU. Due to the better donor ability of DMPU, as quantified by the Gutmann donor numbers,^[23] this ligand exchange is exergonic by $\Delta G_{\text{exch}} = -40.9 \text{ kJ mol}^{-1}$. Subsequent exchange of one of the DMPU ligands by the substrate leads to reactant complex **PRC-I** and is endergonic by $\Delta G_{298} = 26.0 \text{ kJ mol}^{-1}$. In the absence of LiCl this step is significantly more costly, and formation of product complex PRC-II is endergonic by $\Delta G_{298} = 54.5 \text{ kJ mol}^{-1}$. Subsequent reaction barriers are much lower for LiCl-containing transition state TS-I as compared to its LiCl-free analogue TS-II, the difference amounting to $\Delta\Delta G^{\pm}$ (**TS-I/TS-II**) = 48.7 kJ mol⁻¹.^[24]

The main structural difference between these transition states concerns the trajectory angle of the backside attack: while the ideal angle of 180° is nearly reached in TS-I (163°), this is not so in **TS-II** (134°). This indicates that geometrical factors as well as electronic interactions play an important role in decreasing the kinetic barrier. Replacement of the allylic bromide by n-butyl bromide leads to barriers significantly higher in energy $(\Delta \Delta G^{\dagger} (\mathbf{TS-I}) = 29.1 \text{ kJ mol}^{-1}, \Delta \Delta G^{\dagger}$ $(TS-II) = 23.9 \text{ kJ mol}^{-1}$, which is in agreement with the results of the competition experiment of 1-bromononane and (E)-1-bromonon-2-ene (2a). This behavior can be rationalized by inspection of the HOMO and LUMO levels which shows a larger energy difference for the respective aliphatic bromide and an increased substrate deformation energy in the respective transition state.^[25] In conclusion, the presence of LiCl seems essential for fast and selective crosscouplings. In fact, complex mixtures of products are obtained in the absence of LiCl.

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Figure 1. Reaction pathway of the γ , α' -cross-coupling in THF solution (B2PLYP-D3(FC)/def2-TZVPP+ ΔG_{solv} (SMD/B3LYP/6-31G(d)), in kJ mol⁻¹) and graphical representation of the B3LYP/631SVP optimized transition states **TS-I** (\measuredangle C-C_{crot}-Br=163.0°) and **TS-II** (\measuredangle C-C_{crot}-Br=133.9°; bond lengths in pm).

In summary, we have demonstrated that allylic zinc reagents undergo highly regioselective cross-couplings with allylic bromides via an S_N2 -substitution fashion in a 1:1 mixture of THF and DMPU. Furthermore, unsymmetrical allylic zinc reagents undergo this cross-coupling almost exclusively from the most branched side of the allylic system. The stereochemistry of the double bond of the allylic bromide is maintained during the cross-coupling. This S_N2 reaction can be extended to propargylic and benzylic bromides. Further applications are currently underway in our laboratories.

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Keywords: 1,5-dienes \cdot allylic compounds \cdot cross-coupling \cdot S_N2 reaction \cdot zinc

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One of four possible products: Crosscoupling reactions of allylic zinc halides with allylic bromides provide 1,5-dienes with high regioselectivity. Various functional groups (ester, nitrile) are tolerated. Propargylic and benzylic halides can be used in this transformation. DFT calculations confirm the importance of LiCl for

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