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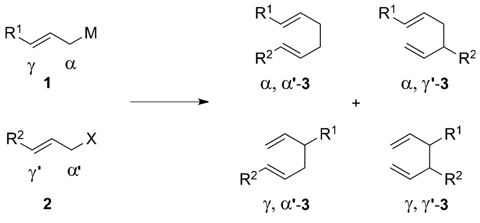
Regioselective Transition-Metal-Free Allyl–Allyl Cross-Couplings

*Mario Ellwart, Ilya S. Makarov, Florian Achrainer, Hendrik Zipse, and Paul Knochel**

***Abstract:** Readily prepared allylic zinc halides undergo S_N2-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 cross-coupling products. Remarkably, the double bond stereochemistry of the allylic halide is maintained during the cross-coupling 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.*

Transition-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 cross-couplings 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 recently, several transition-metal-catalyzed allyl–allyl cross-couplings 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]

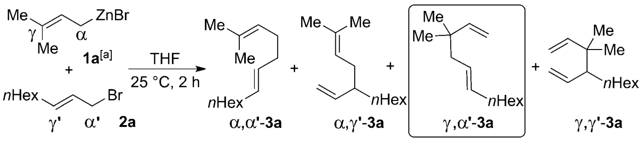


Scheme 1. Cross-coupling of allylic organometallic **1** with allylic halide **2** leading to four regioisomeric coupling products of type **3**.

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 cross-coupling 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 (α,α′/α,γ′/γ,α′/γ,γ′ = 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 γ,α′-**3a**.

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



Entry	T [°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	*n*-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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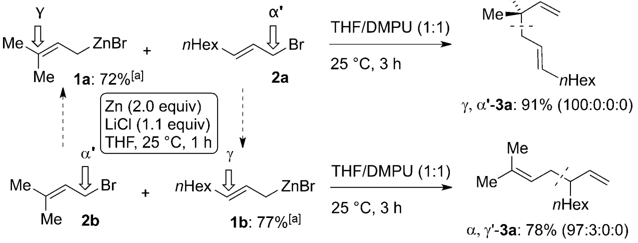
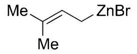
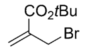
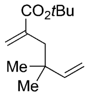
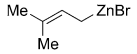
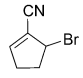
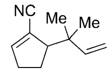
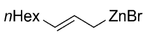
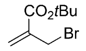
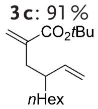
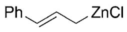
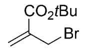
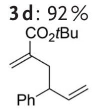
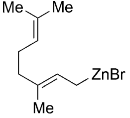
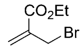
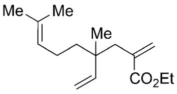
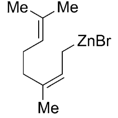
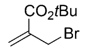
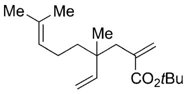
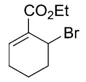
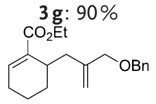
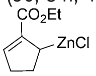
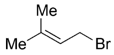
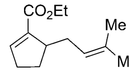
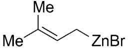
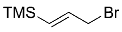
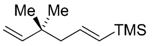
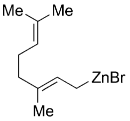
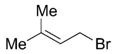
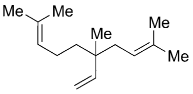
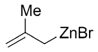
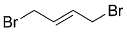
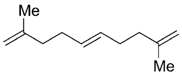
Thus, the use of a 1:1 mixture of THF and unpolar solvents such as toluene (entry 4) and *n*-hexane (entry 5) furnished selectively the cross-coupling product (γ,α′-**3a**) in 89 % and 82 % selectivity, respectively. Switching the solvent to a 1:1 mixture of 1,4-dioxane and THF led to a similar result (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 equivalents 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 (α,γ′-**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).



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,γ′/γ,γ′ ratio). [a] LiCl is omitted for clarity. Yield determined by titration with I_2.

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]
1	 **1a**	 **2c**	 **3b**: 82 %
2	 **1a**	 **2d**	 **3c**: 91 %
3	 **1b** (25, 2 h, 77)	 **2c**	 **3d**: 92 %
4	 **1c** (25, 2 h, 86)	 **2c**	 **3e**: 96 %
5	 **1d** (25, 1 h, 83)	 **2e**	 **3f**: 92 %
6	 **1e** (25, 1 h, 58)	 **2c**	 **3g**: 90 %
7	 **1f** (50, 8 h, 41)	 **2f**	 **3h**: 90 %
8	 **1g** (25, 1 h, 60)	 **2b**	 **3i**: 83 %
9	 **1a**	 **2g**	 **3j**: 79 %
10	 **1d**	 **2b**	 **3k**: 83 %[d]
11	 **1h**[e] (25, 1 h, 66)	 **2h**	 **3l**: 90 %

[a] LiCl is omitted for clarity. In parentheses: temperature, time, yield [%] for the insertion. Yields determined by titration with I_2. [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.

Remarkably, the substituted allylzinc compounds **1f**[15] and **1g**[16] react smoothly with the allylic bromide **2f** 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 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 bromide (**1a**) was treated with the (*E*)- and (*Z*)-allylic bromides **2j**,**k** providing stereoselectively the expected γ,α′-regioisomers (*E*)-γ,α′-**3o** and (*Z*)-γ,α′-**3o** in 76–77 % yield and > 99 % retention of the double bond configuration (Scheme 3).

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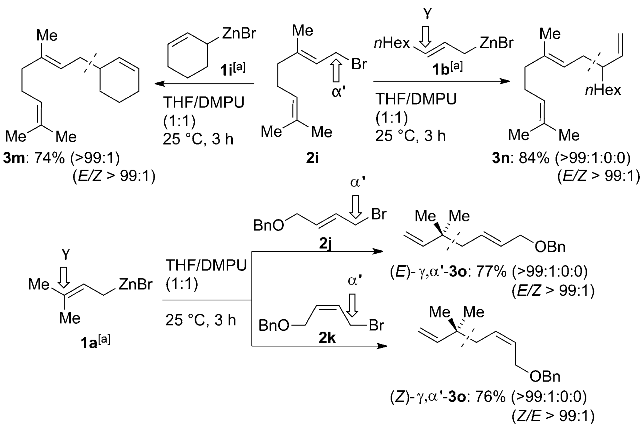
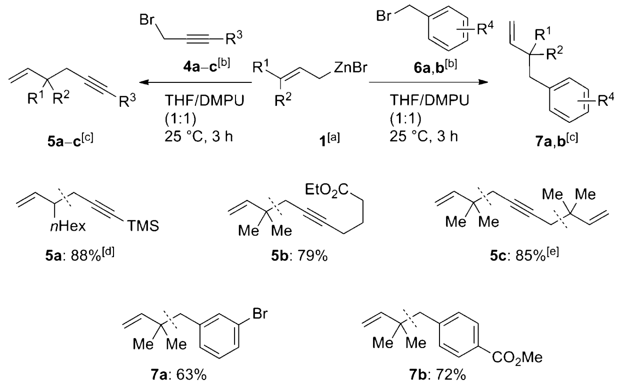


Scheme 3. Allyl–allyl cross-coupling leading to γ,α′-products of type **3** with full retention of the double bond configuration. [a] LiCl is omitted for clarity.

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 $(RZnBr)_2(sol)_2$ ($\Delta G_{sol}(\mathrm{THF}) = -14.4\ \mathrm{kJ\,mol^{-1}}$, $\Delta G_{sol}(\mathrm{DMPU}) = -27.1\ \mathrm{kJ\,mol^{-1}}$) at the B2PLYP-D3(FC)/def2-TZVPP level[19] including implicit SMD/B3LYP/6-31G(d) solvation.[20] Indeed, ^{1}H and ^{13}C NMR shifts in THF obtained during the LiCl-mediated oxidative addition of zinc to the carbon–bromine bond of prenyl 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 $\Delta G_{exch} = -40.9\ \mathrm{kJ\,mol^{-1}}$. Subsequent exchange of one of the DMPU ligands by the substrate leads to reactant complex **PRC-I** and is endergonic by $\Delta G_{298} = 26.0\ \mathrm{kJ\,mol^{-1}}$. In the absence of LiCl this step is significantly more costly, and formation of product complex **PRC-II** is endergonic by $\Delta G_{298} = 54.5\ \mathrm{kJ\,mol^{-1}}$. 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 $\Delta\Delta G^{\neq}$ (**TS-I/TS-II**) $= 48.7\ \mathrm{kJ\,mol^{-1}}$.[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 ($\Delta\Delta G^{\neq}$ (**TS-I**) $= 29.1\ \mathrm{kJ\,mol^{-1}}$, $\Delta\Delta G^{\neq}$ (**TS-II**) $= 23.9\ \mathrm{kJ\,mol^{-1}}$), 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 cross-couplings. In fact, complex mixtures of products are obtained in the absence of LiCl.

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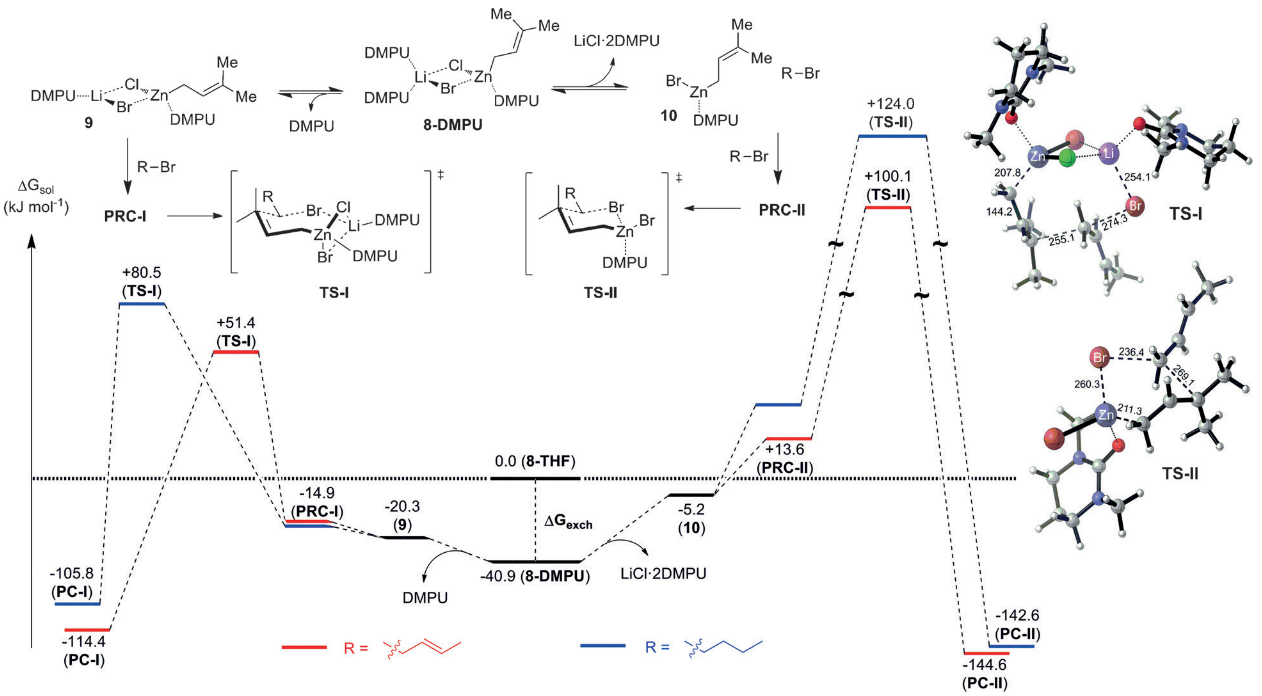

Figure 1. Reaction pathway of the γ,α′-cross-coupling in THF solution (B2PLYP-D3(FC)/def2-TZVPP+ΔG_{solv}(SMD/B3LYP/6-31G(d)), in kJ mol^{-1}) and graphical representation of the B3LYP/631SVP optimized transition states **TS-I** (∡ C-C$_{crot}$-Br = 163.0°) and **TS-II** (∡ C-C$_{crot}$-Br = 133.9°;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