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Enantioselective Sequential Catalytic Arylation-Fukuyama Cross-coupling of 1,1-Biszincioalkane Linchpins

Federico Banchini,^[a] Baptiste Leroux,^[b] Erwan Le Gall,^[b] Marc Presset,^[b] Olivier Jackowski,^{*[a]} Fabrice Chemla,^{*[a]} and Alejandro Perez-Luna^{*[a]}

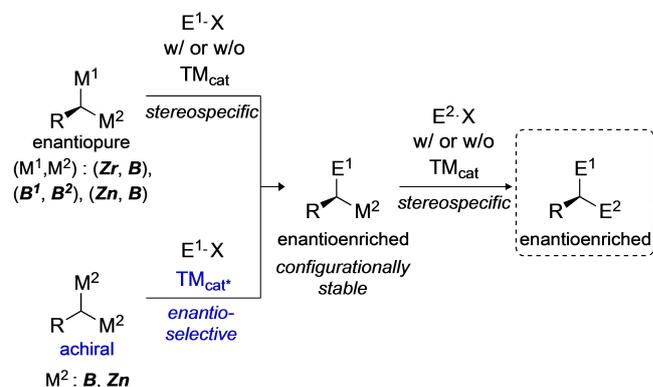
Abstract: 1,1-Bis(iodozincio)alkanes are used as dinucleophilic linchpins in an enantioselective double cross-coupling reaction sequence involving aryl iodides and then thioesters. The two catalytic C–C bond-forming reactions are achieved in the same pot through two distinct palladium-based catalytic systems: a first non-enantioselective one delivering configurationally labile secondary benzylzinc species from an achiral precursor, and a second enantioconvergent one that operates

a highly efficient dynamic kinetic resolution of the racemic intermediates. This strategy, new in the area of asymmetric synthesis through two consecutive electrophilic substitution reactions of geminated C(sp³)-organodimetallics, provides useful methodology to access in a modular fashion acyclic α -disubstituted ketone products with very high enantiomeric purity.

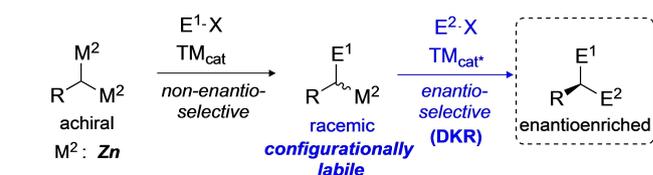
Introduction

Developing tools to achieve the efficient and selective assembly of complex molecular structures with a minimum of chemical steps is a key endeavor in organic synthesis. Organo-*multi*-metallic compounds competent to react sequentially in multiple electrophilic substitution reactions appear ideally suited for this purpose. In this context, geminated C(sp³)-organodimetallics attract pursued interest,^[1] and the opportunity to be engaged in consecutive reactions with two different electrophiles is well established for a variety of such dinucleophilic reagents, amongst which 1,1-diborioalkanes^[2] and 1,1-dizincioalkanes^[3] are particularly well-suited. Conversely, achieving such sequences enantioselectively remains a major challenge.^[4] Two strategies have been reported so far (Scheme 1, top). The first relies on the preparation of chiral non-racemic *gem*-bimetallic reagents which are then engaged in two successive stereospecific reactions. This chemistry was developed with 1,1-diborylalkanes having two boron atoms differentiated by their substitution pattern,^[5–7] as well as with a mixed 1,1-borylzincioalkane^[8,9] and mixed 1,1-borylzincioalkanes.^[10] The

Previous approaches



This work



Scheme 1. Asymmetric synthesis through two consecutive electrophilic substitution reactions of geminated C(sp³)-organodimetallics.

second involves the desymmetrization of achiral *gem*-bimetallic reagents by catalytic enantiotopic group-selective cross-coupling reactions, followed by a subsequent enantiospecific transformation of the chiral non-racemic (mono)organometallic intermediate produced. Here, 1,1-bis(pinacolboronate) esters were engaged in enantioselective palladium-^[11–13] or copper-^[14,15] catalyzed C–C bond-forming reactions which delivered enantioenriched secondary organoboranes suitable for (enantiospecific) C–B bond elaboration. Also, 1,1-bis(iodozincio)ethane was engaged in a one-pot enantioselective Pd-catalyzed allylic alkylation/stereoretentive Cu-mediated

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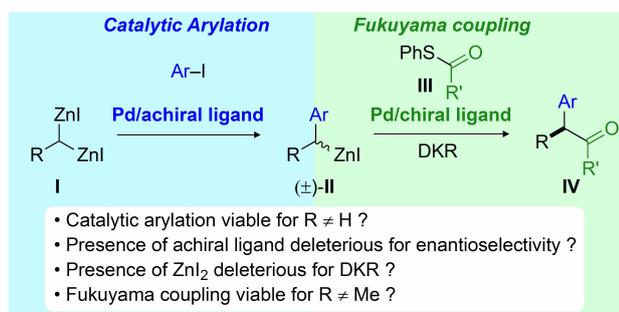
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allenylation sequence,^[3f,16] but ee was low. The key common feature of the two strategies is the involvement of an *enantioenriched configurationally stable* (mono)organometallic intermediate.

Instead, one could envision to rely on a *racemic configurationally labile* (mono)organometallic intermediate by implementing as second step an enantioconvergent reaction ensuring dynamic kinetic resolution (DKR) (Scheme 1, bottom). Here, it is no longer necessary to achieve the desymmetrization of the starting achiral *gem*-dimetallic reagent enantioselectively. Motivated by the reports on stereoselective cross-coupling reactions with configurationally labile secondary organozinc reagents,^[17–19] we reasoned that such an approach, unprecedented to the best of our knowledge, would be ideally suited for 1,1-dizincio bimetals, which in addition have proved so far poor substrates for enantioselective desymmetrization.

We became interested in reports on asymmetric Pd-catalyzed Fukuyama cross-coupling between (1-arylethyl)zinc reagents (II, R=Me) and thioesters (III).^[19] This reaction can deliver in high yields and high enantiomeric purity α -disubstituted ketones IV (R=Me), which are interesting synthetic intermediates. It relies on the efficient DKR of (racemic) benzylic secondary organozinc nucleophiles. In the reported protocols, the organozinc reagents are prepared by reductive zincation of the parent 1-(arylethyl)chlorides. Following on Matsubara's work regarding the selective (mono)arylation of 1,1-bis(iodozincio)methane (I, R=H),^[3f–g] we reasoned that (1-arylethyl)zinc nucleophiles as well as other (1-arylalkyl)zinc intermediates could also be accessed from respectively 1,1-bis(iodozincio)ethane^[3f] and other (yet unknown) 1,1-bis(iodozincio)alkanes upon Pd-catalyzed arylation with aryl iodides (Scheme 2). Such two-step one-pot sequence would provide a more direct and modular entry to the same family of disubstituted ketones with broaden scope: on the one hand, electron-rich aryl moieties, for which access to the requisite 1-(arylethyl)zinc reagents is problematic, could be readily introduced and, on the other hand, ketones IV with an alkyl group R other than methyl could be accessed. The sequential bidirectional coupling strategy faced however several challenges. First, suitable conditions had to be found to achieve the first coupling with good selectivity for the mono-arylation product while suppressing competing β -hydride elimination pathways



Scheme 2. Enantioselective palladium-catalyzed sequenced arylation-acylation of 1,1-bis(iodozincio)alkanes in one pot and associated challenges.

associated to the presence of the alkyl group.^[20] Secondly, stereodifferentiation during the second step had to be achieved despite the presence of the achiral ligand required for the first catalytic system. Third, efficient DKR during the Fukuyama coupling had to be achieved with benzylzinc iodides, which racemize at a slower rate than the benzylzinc chlorides used previously.^[21,22] Last, it remained to be assessed the efficacy in terms of yield and ee of the enantioselective acylation step for benzylzinc intermediates substituted at the benzylic position by alkyl groups other than methyl.

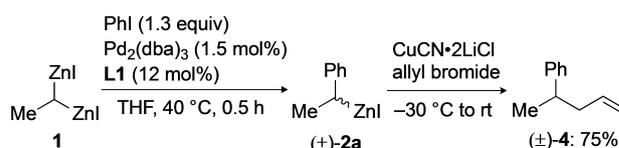
Results and Discussion

Sequential Reactions with 1,1-Bis(iodozincio)ethane as Linchpin

At the outset of our work, we decided to focus on 1,1-bis(iodozincio)ethane (1), and looked first for suitable conditions to accomplish Pd-catalyzed arylations to obtain the corresponding α -methyl-substituted benzylzinc intermediates (II, R=Me), given that such transformation had not been reported previously by Matsubara for 1,1-dizincio bimetals having alkyl substituents.^[3f,g,20] Phenyl iodide was selected as electrophile to produce (±)-2a (Table 1).

The reaction of 1 and phenyl iodide in THF at 40 °C, in the presence of Pd₂(dba)₃ (1.5 mol%) and P[3,5-(CF₃)₂C₆H₃]₃ (L1) (12 mol%), followed by iodolysis, delivered benzyl iodide 3 in 60% yield along with 10–20% of styrene and 4–8% of ethylbenzene. This result demonstrated that substitution at the methylene carbon of the *gem*-bisorganozinc partner was well tolerated. Furthermore, no bis-arylation was detected, substantiating exquisite chemoselectivity towards cross-coupling between the bis-zinc (1) and mono-zinc ((±)-2a) nucleophiles. Further screening allowed us to identify a range of experimental conditions suitable to achieve the cross-coupling reaction with comparable yield (Table 1). Mono-triarylphosphine ligands with diverse electronic characters could be used suitably as ligands, as well as PdCl₂(PPh₃)₂ pre-catalyst. The reaction could also be run conveniently at room temperature but required a longer time for completion. Regarding the reaction solvent, CH₂Cl₂ proved suitable, but not other ethers, nor DMF or DME.

Throughout these optimization studies, 10–20% styrene was detected systematically. This product could arise from β -hydride elimination of an intermediate benzylic palladium complex, but also from iodide 3, following elimination. To shed light on this issue, we also engaged (±)-2a in a copper-mediated allylation reaction (Scheme 3). Product 4 was isolated



Scheme 3. Sequential Pd-catalyzed arylation/Copper-mediated allylation of *gem*-bis(iodozincio)ethane 1 in one pot.

Table 1. Selected reactions of the study of the Pd-catalyzed arylation of **1**.^[a]

| Entry | Variation | Yield [%] ^[b] |
|-------|---|--------------------------|
| 1 | none | 60 ^[c] |
| 2 | rt, 1 h instead of 40 °C, 0.5 h | 55 ^[c] |
| 3 | Pd ₂ (dba) ₃ /L1 = (0.5 mol%/4 mol%) instead of (1.5 mol%/12 mol%) | 51 ^[c] |
| 4 | PPh ₃ instead of L1; rt, 1 h instead of 40 °C, 0.5 h | 59 ^[c] |
| 5 | PdCl ₂ (PPh ₃) ₂ (3 mol%) instead of Pd ₂ (dba) ₃ /L1 | 60 ^[c] |
| 6 | P[4-MeC ₆ H ₄] ₃ instead of L1; rt, 1 h instead of 40 °C, 0.5 h | 61 ^[c] |
| 7 | P[4-(MeO)C ₆ H ₄] ₃ instead of L1; rt, 1 h instead of 40 °C, 0.5 h | 54 ^[c] |
| 8 | CH ₂ Cl ₂ , 1 h instead of THF, 0.5 h | 30 ^[c,d] |
| 9 | CH ₂ Cl ₂ , 4 h instead of THF, 0.5 h | 77 ^[c] |
| 10 | MTBE instead of THF | 40 ^[c] |

[a] All reactions were performed at 0.2 mmol scale. [b] Yield measured prior to purification by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Styrene (10–20%) and ethylbenzene (4–8%) were detected. [d] Only 50% conversion was achieved.

in 75% yield and only traces of styrene were detected, indicating that the yield of formation of (±)-**2a** from **1** is at least 75% and that β-hydride elimination is not a significant competitive process.

The possibility to combine, in the same pot, the arylation reaction leading to intermediate (±)-**2a** with a subsequent Pd-catalyzed enantioselective cross-coupling reaction with thioest-

ers involving chiral non-racemic ligand **L2** was considered next (Table 2). First experiments were carried out with equimolar amounts of substrate **1** and thioester **5a**. We joined the first cross-coupling in THF at 40 °C with the cross-coupling of (±)-**2a** and **5a** under the best conditions reported, i.e., Pd₂(dba)₃ (5 mol%)/**L2** (12 mol%) as catalytic system, at room temperature, in MTBE as solvent (entry 1). Product **6aa** was obtained in

Table 2. Selected reactions of the sequential cross-coupling optimization.

| Entry | Variation 1 st coupling | Variation 2 nd coupling | Yield [%] ^[a] | er ^[b] |
|-------|--|---|--------------------------|-------------------|
| 1 | none | none | 33 | 94:6 |
| 2 | none | THF instead of MTBE | 28 | 93:7 |
| 3 | CH ₂ Cl ₂ instead of THF | CH ₂ Cl ₂ instead of MTBE | < 5% | |
| 4 | CH ₂ Cl ₂ instead of THF | none | 35 | 92:8 |
| 5 | none | + ZnCl ₂ (2.0 equiv.) | 32 | 94:6 |
| 6 | none | + ZnCl ₂ (6.0 equiv.) | 50 | 94:6 |
| 7 | none | + ZnCl ₂ (10.0 equiv.) | 50 | 94:6 |
| 8 | 1.5 equiv. of 1 ^[c] | + ZnCl ₂ (9.0 equiv.) ^[d] | 75 | 94:6 |
| 9 | 1.5 equiv. of 1 ^[c] | + ZnBr ₂ (9.0 equiv.) ^[d] | 67 | 95:5 |
| 10 | 1.5 equiv. of 1 ^[c] | + ZnI ₂ (9.0 equiv.) ^[d] | 64 | 94:6 |
| 11 | 1.5 equiv. of 1 ^[c] | SEt instead of SPh as leaving group ^[d] | 62 | 95:5 |
| 12 | 1.5 equiv. of 1 ^[c] | S(4-NO ₂ -C ₆ H ₄) instead of SPh as leaving group ^[d] | 18 | nc |

[a] Yield measured prior to purification by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [b] Measured by chiral GC. The absolute configuration of **6aa** was determined by comparison with literature data (Ref. [19b]). [c] The amount of PhI and catalyst was adjusted to keep the ratios indicated in the scheme. [d] Pd₂(dba)₃ (7.5 mol%)/**L2** (18 mol%).

33% yield, but high 94:6 er, indicating that the presence of achiral ligand L1 in the reaction media does not preclude high enantiocontrol during the second step. Other solvents and solvent combinations were then surveyed (entries 2–4), including the use of CH₂Cl₂ or THF for both steps or any combination of both, but no yield improvement was achieved. As others,^[19,23] we found that the presence of ZnCl₂ as an additive was highly beneficial for the efficacy of the second coupling (and thus of the whole sequence), provided at least 6.0 equivalents with respect to the *gem*-dizincio reagent **1** were used (entries 5–7). Higher amounts of ZnCl₂ did not afford any further improvement. Added zinc halide salts were reported to enhance conversion and yield in the Fukuyama cross-coupling with organozinc reagents, probably by promoting the formation of zinc-ate complexes more prone to undergo transmetalation.^[23] It was also suggested with chiral secondary organozincs,^[19b] that ZnCl₂ could accelerate the rate of racemization of the organometallic. In our system, such does not seem to be a critical role because, on the one hand, no difference of er was noted for reactions performed in the presence or in the absence of the ZnCl₂ additive and, on the other hand, no difference of kinetics nor yield was observed between reactions with racemic or enantiopure ligands carried out either in presence or in the absence of ZnCl₂.

Finally, while keeping the very high levels of enantioselectivity, a synthetically valuable 75% yield in product **6aa** from **5a** was achieved using a slight excess of *gem*-dizincio reagent **1** to work with substrate/reagent ratios that are typical for the Fukuyama cross-coupling (entry 8).^[19,23] Interestingly, the nature of the zinc counter-anion does not seem to have a decisive effect on the reaction outcome, given that quite similar results were obtained using ZnI₂ or ZnBr₂ as additives (entries 9 and 10). Modulation of the thioester leaving group was also investigated with this protocol (entries 11 and 12). With ethyl instead of phenyl, a still good 62% yield with 95:5 er was achieved, whereas with 4-nitrophenyl, almost no reaction was obtained.

With the best conditions identified (Table 1, entry 8), we then established the scope of the tandem reaction (Scheme 4). Regarding the aryl iodide partner, *para*- and *meta*-substituted derivatives were well tolerated in the sequence, delivering ketones **6aa–6ga** and **6ka** in 57–86% yield, regardless of the electronic character (electron-donating or electron-withdrawing) of the substituents. *Ortho*-substitution at the aryl ring, which was not disclosed in previous reports, also proved feasible (**6ia**, **6ja**, **6la**), albeit with a moderate drop of yield (~55%). In the particular case of 2-methoxy-substituted aryl iodides, lower enantioselectivity was also noted. By contrast, *ortho*-disubstituted aryl iodides were not competent, a result that is in line with the observed efficacy loss of the Fukuyama cross-coupling reaction with increased steric hindrance. Aryl iodides derived from more extended aromatic moieties performed very well, leading to 2-naphtyl (**6na**, **6oa**)- or 2-fluorenyl (**6pa**) products in high yield and enantiocontrol. Finally, the sequence was tested with heteroaromatic iodides (formation of indolyl (**6qa**)- or thiophen-3-yl (**6ra**) products), but proved less efficient (yet viable).

Variation of the thioester partner was also possible. Thioesters with secondary alkyl substituents led consistently to high yields and enantioselectivities, as shown with the formation of products **6bb–6bf**. Cyclopropyl- (**6bg**), methyl- (**6bh**), linear alkyl- (**6bi**) and 2-furyl (**6bj**) ketones were also formed in quite good yields but only moderate (~75:25) er. By contrast, more hindered products such as *tert*-butyl ketone **6bk** were produced in very low yields, if at all.

Sequential reactions with other 1,1-bis(iodozincio)alkane linchpins

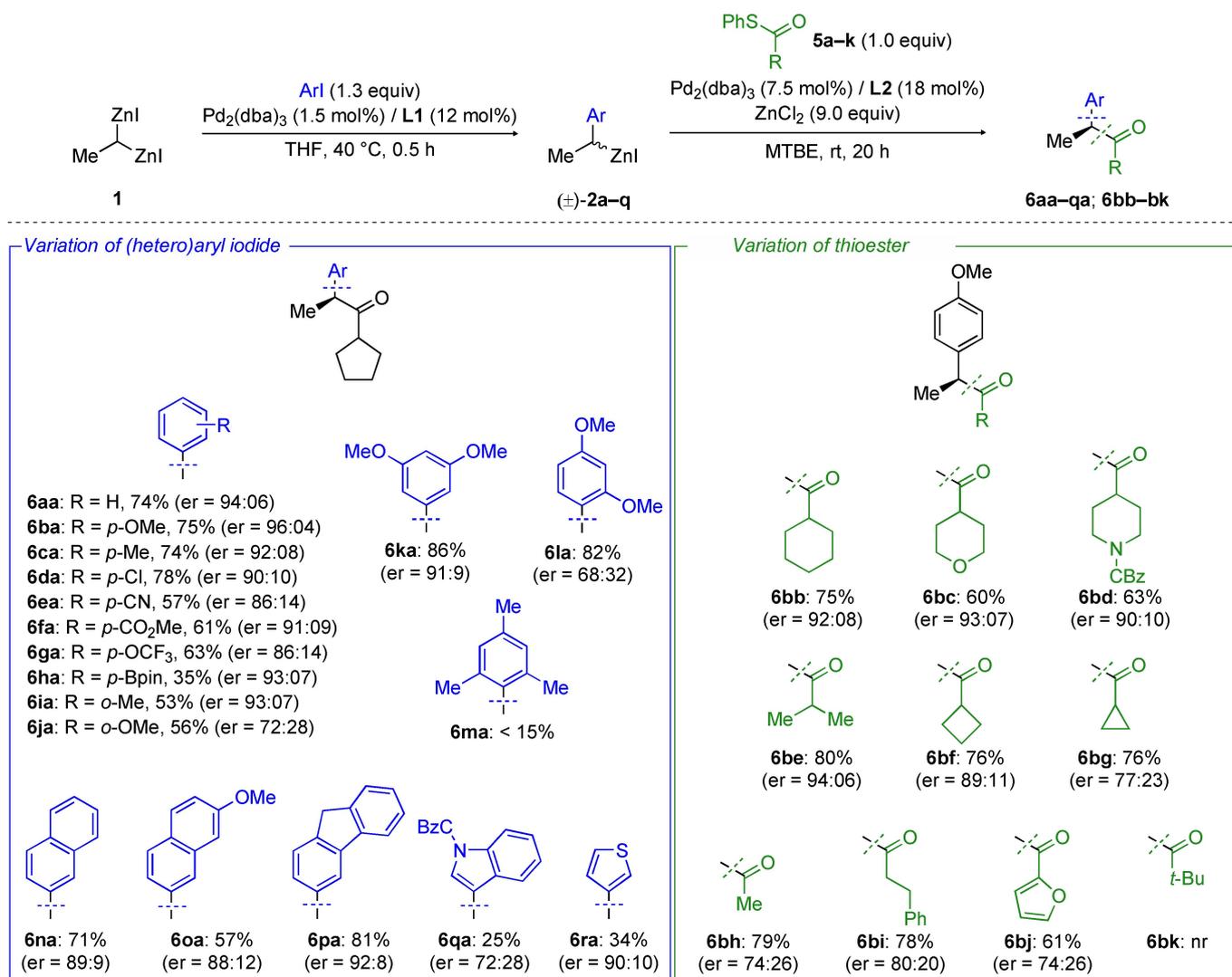
In the last part of our work, we evaluated the potential as linchpins of 1,1-dizincio bimetallics having different primary alkyl substituents at the methylene carbon. THF solutions of 1,1-bis(iodozincio)alkanes **7–9** were readily prepared from the parent 1,1-diiodo compounds on treatment with zinc dust in the presence of PbCl₂ (2 mol%).

The experimental conditions developed for the Pd-catalyzed (mono)arylation of **1** proved suitable for 1,1-bis(iodozincio)alkanes **7–9**. Cross-coupling with phenyl iodide delivered organozinc intermediates (\pm)-**10a–12a** that could then be engaged in a copper-promoted allylation reaction leading to products **13–15** in 77–87% yields (Scheme 5). The latter provide a good estimate (lower limit) of the yield for the arylation reaction.

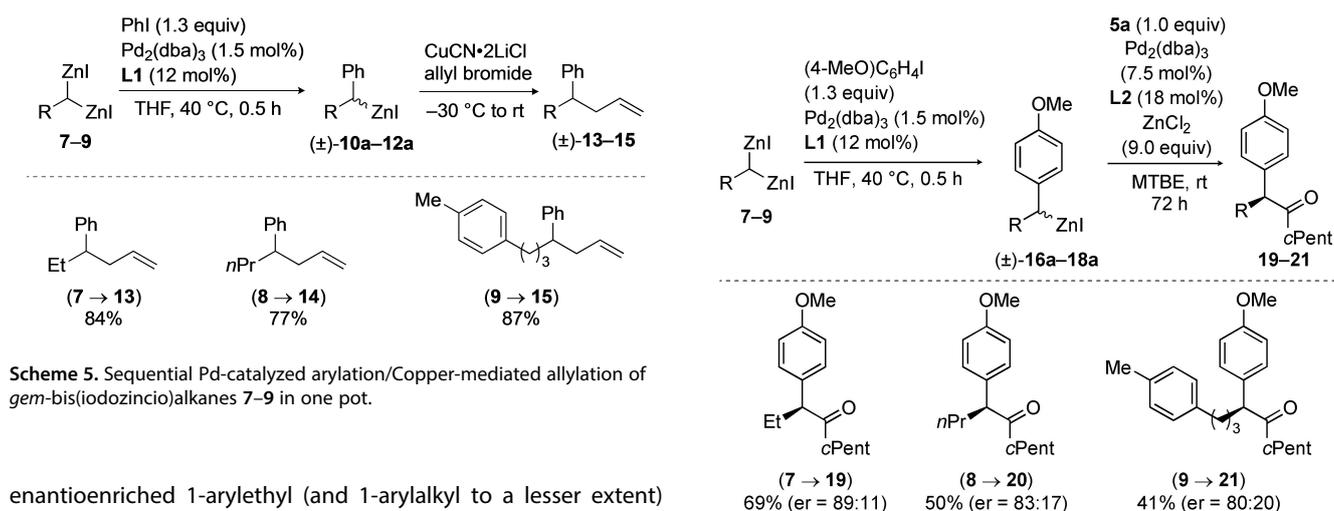
The protocol for enantioselective sequential arylation-acylation was then considered with Et-substituted linchpin **7** using as electrophilic partners 4-methoxyiodobenzene and thioester **5a** (Scheme 6). Product **19** was obtained in high 89:11 er, but only a low 26% yield after 20 h of reaction time for the acylation step. The yield was nevertheless improved to satisfactory levels (69%) by increasing the reaction time of the Fukuyama step (72 h). The same conditions were applied to 1,1-bis(iodozincio)alkanes **8** and **9** that have longer alkyl chains. Double-coupling products **20** and **21** were obtained in decent er and yield, in spite of a gradual erosion with increasing length of the alkyl substituents. These results are particularly significant because they represent the first examples of enantioselective Fukuyama cross-coupling involving organozinc partners other than (1-arylethyl)zinc derivatives.

Conclusions

In conclusion, we have developed a one-pot sequential enantioselective double cross-coupling reaction of 1,1-dizincio reagents entailing arylation and acylation with two distinct Pd-based catalytic systems. Mechanistically, the approach relies on a first step involving the (non-enantioselective) desymmetrization of an achiral geminated C(sp³) bimetallic reagent that delivers a stereolabile monometallic intermediate that undergoes efficient dynamic kinetic resolution during the subsequent second step. Our report represents the first example of implementation of such a strategy for asymmetric synthesis. Synthetically, we disclose a modular access to important



Scheme 4. Reaction scope for the enantioselective sequential arylation/Fukuyama cross-coupling reaction of 1,1-bis(iodozincio)ethane **1**.



enantioenriched 1-arylethyl (and 1-arylalkyl to a lesser extent) ketones, including products with electron-rich aryl units which had not been accessed previously through direct Fukuyama cross-coupling reactions. As part of this work, we also establish on the one hand that Matsubara's Pd-catalyzed (mono)arylation

of *gem*-bisorganozinc reagents tolerates the presence of H-atoms β to the metal and can thus be used conveniently with 1,1-bis(iodozincio)alkanes other than 1,1-bis(iodozincio)methane, and on the other hand that asymmetric Fukuyama cross-coupling reactions can be extended beyond (1-arylethyl) organozincs.

Experimental Section

General procedure for the preparation of 1,1-(diiodozincio)alkanes (1, 7–9): To a THF (1 mL) suspension of Zn dust (1.3 g, 20 mmol) and PbCl_2 (28 mg, 0.1 mmol) under argon atmosphere, was added trimethylsilylchloride (0.05 mL, 0.4 mmol), and the mixture was stirred for 10 min at rt. The mixture was cooled down to 0 °C and was added dropwise a THF (4 mL) solution of 1,1-diiodoalkane (5 mmol) over 2 h. After complete addition, the resulting mixture was stirred for 3 h at rt. The excess of zinc was removed by centrifugation and the supernatant was transferred in an oven-dried flask and stored under a positive pressure of argon at –20 °C. The reagent was titrated with I_2 [24] THF solutions of reagents **1**, **7**, **8** and **9** with concentrations of ~0.4–0.7 M were routinely obtained.

General procedure for the sequential Pd(0)-catalyzed arylation-copper-mediated allylation of 1,1-bis(iodozincio)alkanes (Schemes 3 and 5): An oven-dried flask under argon was charged with $\text{Pd}_2(\text{dba})_3$ (2.7 mg, 0.003 mmol) and **L1** (16.1 mg, 0.024 mmol). A solution of iodoarene (0.26 mmol) in THF (0.5 mL) was added. The mixture was stirred for 5 min at rt before a solution of 1,1-diiodozincioalkane (0.2 mmol) was added slowly. The resulting mixture was stirred for 0.5 h at 40 °C. Then the reaction mixture was cooled down to –30 °C, a solution of $\text{CuCN} \cdot 2\text{LiCl}$ (0.22 mL, 1.0 M in THF, 0.22 mmol) was added dropwise and the resulting mixture was stirred at the same temperature for 20 min. After that, a THF (0.3 mL) solution of allyl bromide (48 mg, 0.40 mmol) was added dropwise at –30 °C and the reaction mixture was stirred overnight letting it return to rt. The reaction was quenched with saturated NH_4Cl solution (4 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel.

General procedure for the Pd(0)-catalyzed enantioselective sequential arylation-Fukuyama cross-coupling of 1,1-bis(iodozincio)alkanes (Schemes 4 and 6): An oven-dried flask under argon was charged with $\text{Pd}_2(\text{dba})_3$ (4.1 mg, 0.0045 mmol) and **L1** (24.1 mg, 0.036 mmol). A solution of aryl iodide (0.39 mmol) in THF (0.5 mL) was added. The mixture was stirred for 5 min at rt before a solution of 1,1-diiodozincioalkane (0.4–0.7 M in THF, 0.3 mmol) was added slowly. The resulting mixture was stirred for 0.5 h at 40 °C. Then the reaction mixture was cooled down to rt and was added ZnCl_2 (1.2 mL, 1.5 M in THF, 1.8 mmol) and the mixture was stirred for 30 min. After that, another oven-dried flask under argon was charged with $\text{Pd}_2(\text{dba})_3$ (13.7 mg, 0.015 mmol) and **L2** (41.4 mg, 0.036 mmol) and MTBE (1.8 mL). The solution was stirred for 10 min at rt after which was added a solution of the appropriate thioester (**5**) (0.2 mmol) in THF (0.4 mL), and the reaction mixture from the first cross-coupling via cannula. The reaction was stirred at r.t. for 20 h or 72 h, after which it was quenched with HCl (4 mL, 1 M) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with NaOH (1 M) and brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel.

Supporting Information: The authors have cited additional references within the Supporting Information.^[25–46]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: bimetallics · cross-coupling · enantioselectivity · tandem reactions · zinc

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