C–C Coupling

Deutsche Ausgabe: DOI: 10.1002/ange.201608535
Internationale Ausgabe: DOI: 10.1002/anie.201608535

Terminal-Selective Functionalization of Alkyl Chains by Regioconvergent Cross-Coupling

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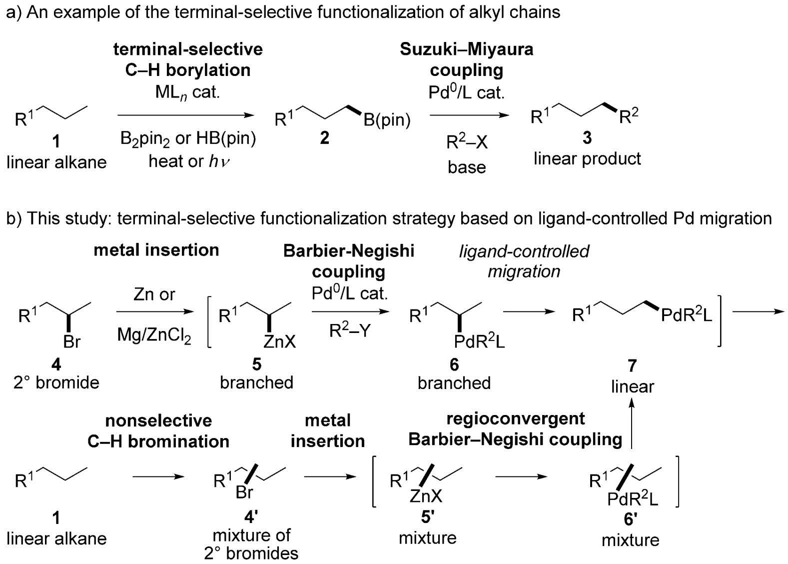
Abstract: *Hydrocarbons are still the most important precursors of functionalized organic molecules, which has stirred interest in the discovery of new C–H bond functionalization methods. We describe herein a new step-economical approach that enables C–C bonds to be constructed at the terminal position of linear alkanes. First, we show that secondary alkyl bromides can undergo in situ conversion into alkyl zinc bromides and regioconvergent Negishi coupling with aryl or alkenyl triflates. The use of a suitable phosphine ligand favoring Pd migration enabled the selective formation of the linear cross-coupling product. Subsequently, mixtures of secondary alkyl bromides were prepared from linear alkanes by standard bromination, and regioconvergent cross-coupling then provided access to the corresponding linear arylation product in only two steps.*

The direct functionalization of hydrocarbon chains is a step-economical approach to functionalized organic intermediates rich in tetrahedral carbon atoms from cheap and abundant feedstocks, and has become a topic of intense investigation.[1] Two main strategies based on transition-metal catalysis have been pursued to tackle this challenging synthetic problem:[2] inner-sphere C–H activation, involving concerted C–H bond cleavage and carbon–metal bond formation, and outer-sphere C–H activation, which does not involve organometallic intermediates. These two strategies show distinct selectivity profiles. In most reported inner-sphere reactions, a directing group is used to control the site selectivity of C–H bond cleavage, whereas nondirected methods are scarce.[1b] The transition-metal-catalyzed C–H borylation reactions developed by Hartwig and co-workers constitute notable examples, wherein the terminal-selective activation and functionalization of alkyl chains is achieved by steric control (Scheme 1 a).[3,4] This borylation reaction can be followed by a palladium-catalyzed Suzuki–Miyaura cross-coupling to create a C–C bond at the same position (**2**→**3**), with the inconvenience that two noble metals are employed in this two-step sequence.[5] A conceptually different strategy is reported herein (Scheme 1 b).

Secondary bromoalkanes **4** are readily available compounds, which can be generated by the bromination of abundant feedstocks, such as alkenes, alcohols, or even alkanes **1**. The generation of an alkyl zinc halide **5** from **4** by metal insertion,[6] followed by transmetalation to an organopalladium complex [Pd(R^2)YL] generated in situ, would form the corresponding branched alkyl palladium intermediate **6**. The organopalladium species would migrate to the terminal position (→**7**) through a succession of β-H elimination, rotation, and insertion steps induced by a suitable ancillary ligand, and would then undergo reductive elimination to give the linear product **3**.[7,8]



Scheme 1. Two conceptually different strategies for the terminal-selective functionalization of alkyl chains.

Ligand-controlled palladium(0)-catalyzed migrative coupling reactions have been investigated by our research group

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201608535.

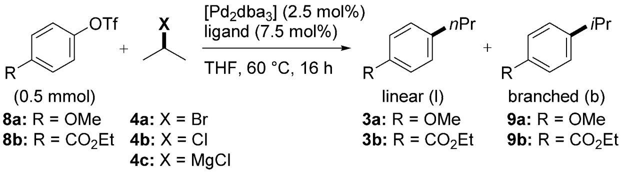
by the use of enolates as nucleophiles[9] or organozinc compounds obtained by *tert*-butoxycarbonyl (Boc)-directed lithiation and Li–Zn transmetalation.[10] Herein, we show that terminal (linear) cross-coupling products **3** can be obtained in a regioconvergent manner in just one step from bromoalkanes **4** under operationally simple Barbier (in situ) conditions. Furthermore, in most cases a similar selectivity pattern was observed regardless of the position of the bromine atom in the alkyl chain. This observation led us to employ mixtures of bromides **4′** obtained by the radical bromination of linear alkanes **1**. Indeed, this process is known to give rise to mixtures of secondary bromides,[11] and hence has been of little synthetic use so far. However, we reasoned that such a mixture could be productively utilized by applying the same in situ metal-insertion/migrative Negishi coupling sequence: A mixture of branched organopalladium intermediates **6′** would converge to the same linear complex **7**, thereby furnishing the same linear product **3**.

At the outset of our studies, we sought suitable and practical conditions for the generation (**4**→**5**) and cross-coupling (**5**→**3**) of alkyl zinc reagents in situ to maximize the overall step economy. Such direct Barbier–Negishi coupling reactions have been reported by Lipshutz and co-workers, who employed water as the solvent and a diamine as an additive, either in the presence of a surfactant[12] or under "on-water" conditions.[13] An improved catalytic system that enables a range of cyclic bromoalkanes to be coupled with aryl electrophiles was recently disclosed by Buchwald and co-workers.[14] However, to the best of our knowledge, alkyl–aryl coupling under non-aqueous Barbier conditions has not been reported.[15,16] We reasoned that aryl triflates (Y = OTf) would be suitable electrophiles, since they should not undergo zinc insertion, and therefore should show orthogonal reactivity to alkyl halides **4**. Hence, we started to investigate the coupling of aryl triflate **8a** with an excess amount of the organozinc reagent generated from 2-bromopropane (**4a**), zinc dust, and LiCl in THF,[6a] in the presence of a Pd catalyst formed in situ from [Pd$_2$dba$_3$] and a suitable phosphine ligand (Table 1). The choice of the latter was guided by our previous studies on migrative Negishi coupling reactions, wherein flexible phenylazole-based ligands were found to induce the highest selectivity in favor of the linear product.[10]

We tested a library of homemade ligands from this family (see Table S1 in the Supporting Information) and found that the phenyl–pyrrole-based phosphine **L^1** containing *n*-butyl P substituents provided the highest linear selectivity, presumably owing to its high degree of flexibility at both the phenyl–pyrrole and the P–alkyl bonds. Gratifyingly, the use of Pd (5 mol %) and **L^1** (7.5 mol %), which is readily synthesized in one step from *N*-phenylpyrrole, led to a mixture of the linear product **3a** and branched product **9a** with good selectivity (9:1), albeit in very low yield, presumably as a result of slow zinc insertion (Table 1, entry 1).

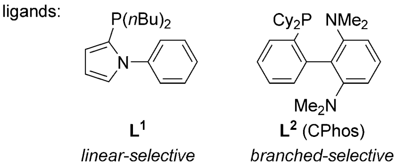
We thus looked for conditions that would allow the organozinc intermediate to be generated more rapidly. Gratifyingly, when we carried out the reaction under conditions described by Knochel and co-workers with a mixture of Mg, LiCl, and ZnCl$_2$,[6b] the yield was greatly improved, and the good linear/branched (l/b) selectivity was maintained (entry 2). Interestingly, similar results were observed with 2-bromopropane (**4a**) or 2-chloropropane (**4b**) when zinc chloride was omitted (entries 3 and 4). A control experiment with the commercially available, preformed Grignard reagent **4c** also led to a similar outcome (entry 5). Notably, 2-chloropropane also proved a competent reactant in the presence of ZnCl$_2$, although the yield of the reaction was lower (entry 6). Importantly, when the more rigid and bulky phosphine **L^2** developed by Buchwald and co-workers was employed,[17] the selectivity was completely reversed, thus leading exclusively to the branched product **9a** in 82 % yield (Table 1, entry 7). These results highlight the role of the ligand in the linear/branched selectivity control. Moreover, they show that both linear and branched products can be synthesized in a divergent manner from the same reactants by choosing a different ligand.

Table 1: Linear-selective Barbier–Negishi coupling: Optimization of the reaction conditions.

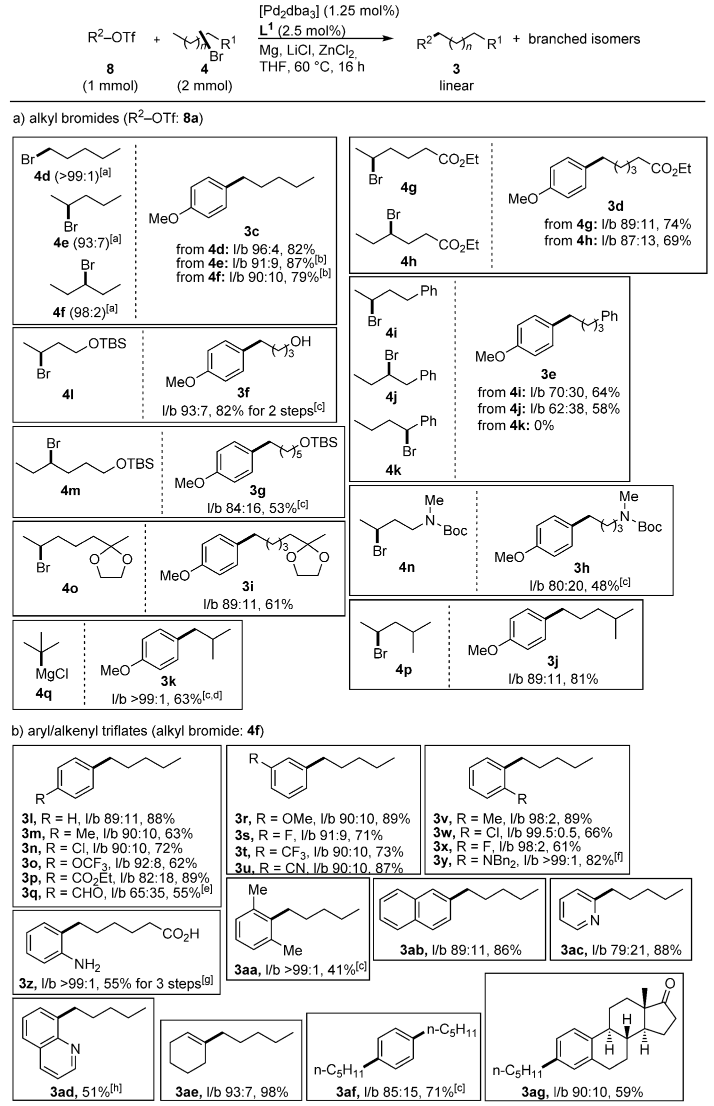


Entry	Organometallic reagent (equiv)	R	Ligand	l/b[a]	Yield of **3** [%][b]
1	**4a**/Zn/LiCl (2)	OMe	**L^1**	90:10	18
2	**4a**/Mg/LiCl/ZnCl$_2$ (4)	OMe	**L^1**	91:9	73 (91)[c]
3	**4a**/Mg/LiCl (4)	OMe	**L^1**	87:13	52
4	**4b**/Mg/LiCl (4)	OMe	**L^1**	89:11	62
5	**4c**/LiCl (1.3)	OMe	**L^1**	88:12	72
6	**4b**/Mg/LiCl/ZnCl$_2$ (4)	OMe	**L^1**	92:8	45
7	**4a**/Mg/LiCl/ZnCl$_2$ (4)	OMe	**L^2**	< 2:98	82[d]
8	**4a**/Mg/LiCl (4)	CO$_2$Et	**L^1**	63:37	< 10
9	**4a**/Mg/LiCl/ZnCl$_2$ (4)	CO$_2$Et	**L^1**	87:13	76[c]
10	**4a**/Mg/LiCl/ZnCl$_2$ (2)	OMe	**L^1**	92:8	82 (83)[c]
11[e]	**4a**/Mg/LiCl/ZnCl$_2$ (2)	OMe	**L^1**	92:8	76 (80)[c]
12[f]	**4a**/Mg/LiCl/ZnCl$_2$ (2)	OMe	**L^1**	92:8	66 (64)[c]

[a] The linear/branched ratio was measured by GCMS. [b] The yield was determined by GCMS with tetradecane as an internal standard. [c] Yield of the isolated mixture of linear/branched products. [d] Yield of the isolated branched product **9a**. [e] Catalyst loading: 1.25 mol % [Pd$_2$dba$_3$]/2.5 mol % **L^1**. [f] Catalyst loading: 0.625 mol % [Pd$_2$dba$_3$]/1.25 mol % **L^1**. dba = dibenzylideneacetone, Tf = trifluoromethanesulfonyl.



The reaction of aryl triflate **8b** containing the more electrophilic ester substituent was next studied to further probe the utility of the Mg-to-Zn transmetalation (Table 1, entries 8 and 9). As suspected, the addition of ZnCl$_2$ proved to be crucial for the desired coupling (entry 9), since only a small amount of the coupling product was observed in its absence (entry 8). These results show that ZnCl$_2$ can be omitted for less sensitive substrates, such as **8a** (entries 3–5), but also that the Mg/LiCl/ZnCl$_2$ system provides better chemoselectivity and versatility. Final refinements of the reaction conditions were made by diminishing the quantity of the organozinc reagent generated in situ to 2 equivalents (entry 10), and by lowering the catalyst loading to 2.5 mol % Pd and ligand (entry 11). A further decrease in the loading to 1.25 mol % Pd was found to be viable, but the yield was lower (entry 12). Finally, reactions of **8a** with deuterated 1- and 2-bromopropane showed pronounced deuterium scrambling over the three carbon atoms, thereby indicating that palladium migrates in a reversible fashion along the alkyl chain (see Figure S1 in the Supporting Information).



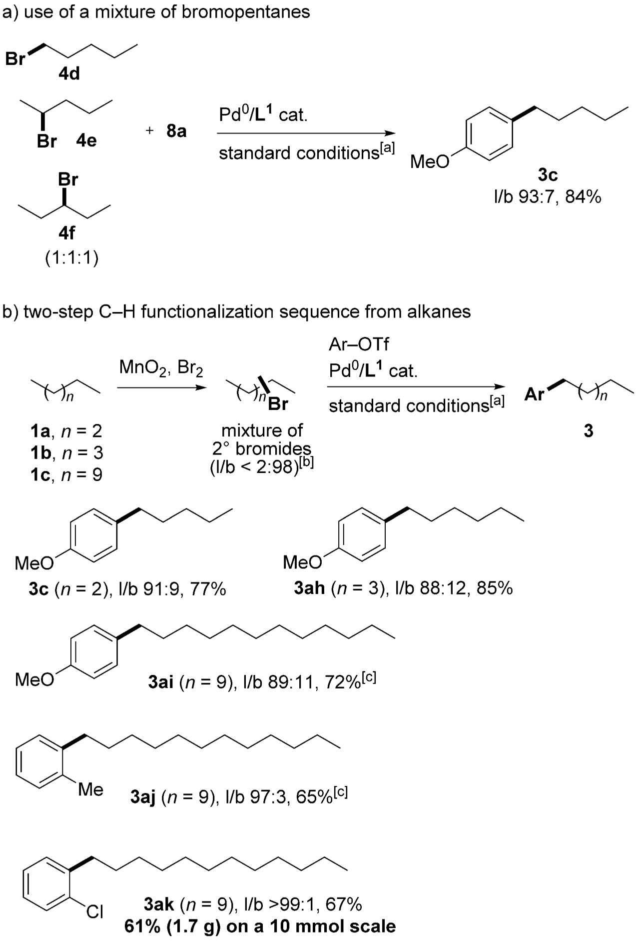
Scheme 2. Scope and limitations of the regioconvergent cross-coupling. Standard reaction conditions: R^2OTf **8** (1 mmol), alkyl bromide **4** (2 equiv), Mg (2 equiv), LiCl (2 equiv), $ZnCl_2$ (2 equiv), [Pd_2dba_3] (1.25 mol%), **L^1** (2.5 mol%), THF, 60 °C, 16 h. Linear/branched ratios were measured by GCMS. Yields refer to the isolated linear/branched mixture. [a] Isomeric purity of the starting bromide, as determined by GCMS; for **4e** and **4f**, the minor isomer was the other secondary bromide. [b] With **L^2** as the ligand, a mixture of 2- and 3-aryl pentanes was obtained in ratios of 93:7 for **4e** and 30:70 for **4f**, with no trace of the linear product **3c**. [c] Catalyst loading: 2.5 mol% [Pd_2dba_3]/5 mol% **L^1**. [d] With **L^2** as the ligand, a 2:1 mixture of **3k**/anisole was obtained. [e] The reaction was carried out with 4 equivalents of $ZnCl_2$. [f] With **L^2** as the ligand, the l/b ratio was 73:27. [g] 1) Migrative cross-coupling; 2) H_2, Pd/C, EtOH (55% for 2 steps); 3) LiOH, THF/H_2O (quant.). [h] Yield of the pure linear product; in this case, the l/b ratio could not be determined. Bn = benzyl, Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

The generality of the reaction was next studied under the optimal conditions (2.5 mol % Pd; Scheme 2). The catalyst loading was doubled when incomplete conversion was observed. We first investigated the reactivity and selectivity of structurally diverse linear alkyl bromides that were either commercially available or could be synthesized in a few steps by standard chemistry, with triflate **8a** as an electronically and sterically unbiased electrophile (Scheme 2 a). All three isomers of bromopentane (**4d**–**f**) gave rise to the same coupling product **3c** with l/b selectivity above 90:10 in the presence of ligand **L^1**. In contrast, the replacement of **L^1** with CPhos (**L^2**) led to a mixture of both branched products, and no linear product was observed. The more sensitive bromoesters **4g**,**h** furnished product **3d** with slightly reduced selectivity (89:11 and 87:13). However, these examples further demonstrate the good chemoselectivity of this process. Surprisingly, the isomeric bromides **4i**,**j** containing a phenyl ring led to the major linear product **3e** with significantly different selectivity. Moreover, the reaction of bromide **4k** did not give any coupling product. These results suggest that the presence of a benzylic position on the alkyl chain disfavors both Pd migration and the C−C reductive elimination. Besides an ethyl ester (product **3d**), the reaction was found to be compatible with other useful functional groups, such as a TBS-protected alcohol (bromides **4l**,**m**), a Boc-protected secondary amine (product **3h**), and an acetal (product **3i**). In particular, the TBS-protected bromide **4l** was converted into alcohol **3f** in excellent yield (82 % for two steps after acid-mediated deprotection of the TBS group) and selectivity (l/b 93:7). The migrative arylation of the longer-chain TBS-protected bromoalcohol **4m**, in which the bromine atom was installed at a more central position of the alkyl chain (similar to **4h**), also proceeded in acceptable yield with good selectivity. Interestingly, the reaction of 2-bromo-4-methylpentane (**4p**), containing a tertiary carbon atom, led to compound **3j** as the sole linear product in good yield with 89 % selectivity. No trace of the other possible linear product was observed, thereby indicating that branching arrests Pd migration along the alkyl chain.

Tertiary halides, such as *tert*-butyl bromide and iodide, failed to react under the same Barbier-type conditions. We hypothesized that this lack of reactivity might originate from the Mg insertion step, which is known to be very slow with tertiary halides.[18] Hence, we directly engaged commercially available *tert*-butylmagnesium chloride (**4q**), which indeed gave rise to the corresponding linear product **3k** in 63 % yield with no trace of the branched product. The same selectivity in favor of the linear product was observed with ligand **L^2**; thus, the reaction is essentially substrate-controlled with this substrate. However, when $\mathbf{L}^2$ was used, the product **3k** was accompanied by large amounts of anisole and could not be isolated from the crude mixture. Therefore, ligand $\mathbf{L}^1$ seems to be the most suitable ligand for tertiary substrates as well.

Next, the scope of the reaction with regard to the triflate was investigated with 3-bromopentane (**4f**) as the alkyl bromide (Scheme 2b). The reaction conditions were found to be compatible with a variety of electron-poor and electron-rich substituents at the *para* (products **3l–p**) and *meta* positions (**3r–u**), thereby providing the linear product in good yield (62–89%) and l/b selectivity (82:18–92:8). A chlorine atom (product **3n**) and electrophilic ester and nitrile functional groups (products **3p**,**u**) were well tolerated. Even the more electrophilic aldehyde **3q** could be obtained, albeit in lower yield and with lower selectivity despite the use of a larger excess of $ZnCl_2$ to prevent the nucleophilic addition of the Grignard intermediate. Higher l/b ratios were observed when *ortho* substituents were present (products **3v–y**), consistent with previous studies.[9,10] A control experiment with ligand $\mathbf{L}^2$ showed that the selectivity is both substrate- and ligand-controlled in this case (for product **3y**: l/b >99:1 with $\mathbf{L}^1$ and 73:27 with $\mathbf{L}^2$). An interesting combination of an alkyl bromide and an aryl triflate—bromoester **4g** and *ortho*-dibenzylaminophenyl triflate—enabled the synthesis of the original η-amino acid **3z** in 55% overall yield for three steps after hydrogenation and ester hydrolysis. Other interesting aryl triflates used included those containing two *ortho* substituents (product **3aa**), a naphthyl ring (product **3ab**), and a heteroarene (products **3ac–ad**). Furthermore, as shown with product **3ae**, the reaction is not limited to (hetero)aryl triflates: Cyclohexenyl triflate also gave excellent results (l/b 93:7, 98%). A bistriflate reacted at both positions to give the double cross-coupling product **3af** in good yield with good selectivity. Finally, a more complex estrone-derived triflate reacted successfully to give **3ag**.

As a proof-of-concept experiment toward the development of a two-step linear-selective functionalization of alkanes, an equimolar mixture of bromopentanes **4d–f** was prepared and treated with aryl triflate **8a** under the standard cross-coupling conditions (Scheme 3a). The yield of the corresponding linear product **3c** (84%) and the selectivity of the reaction (l/b 93:7) were consistent with the results obtained with isolated bromopentanes (see Scheme 2a, top left). This result suggested that the same principle would be applicable to the regioconvergent coupling of mixtures of alkyl bromides of different molar compositions, synthesized by alkane bromination. To test this hypothesis, the non-selective radical monobromination of three linear alkanes **1a–c** was performed in an efficient and scalable manner with Br_2/MnO_2 as a convenient system,[19] and the resulting mixtures of secondary alkyl bromides were used in the migrative cross-coupling with various electrophiles (Scheme 3b). Excellent results were observed with *n*-pentane (**1a**), *n*-hexane (**1b**), and even dodecane (**1c**), which furnished the five linear products **3c**, **3ah**, and **3ai–ak**, respectively, with good to high l/b selectivity, depending on the aryl triflate used. Gratifyingly, the scale of the bromination/regioconvergent coupling to give product **3ak** could be increased tenfold without a significant decrease in efficiency (61% yield with 10 mmol of the aryl triflate versus 67% with 1 mmol of the aryl triflate).



Scheme 3. Development of a two-step functionalization of linear alkanes. Linear/branched ratios were measured by GCMS. Yields refer to the isolated linear/branched mixture. [a] ArOTf (1 mmol), mixture of alkyl bromides (2 equiv), Mg (2 equiv), LiCl (2 equiv), $ZnCl_2$ (2 equiv), $[Pd_2dba_3]$ (1.25 mol%), $\mathbf{L}^1$ (2.5 mol%), THF, 60°C, 16 h. [b] Isomeric composition for pentane: 2-bromopentane/3-bromopentane (79:21); for hexane: 2-bromohexane/3-bromohexane (59:41); for dodecane: mixture of five secondary bromododecane isomers (19:17:20:18:26). [c] Catalyst loading: 2.5 mol% $[Pd_2dba_3]$/5 mol% $\mathbf{L}^1$.

In conclusion, we have developed a cross-coupling method based on ligand-induced Pd migration for the synthesis of functionalized alkanes from readily accessible branched alkyl bromides with good to high selectivity for the linear product. Highly practical Barbier-type conditions were devised for the in situ generation and cross-coupling of the intermediate organozinc species. Various positional isomers of the same alkyl bromide gave rise to the linear cross-coupling product with comparable selectivity. This regioconvergent coupling was coupled to a nonselective radical monobromination step, thereby enabling the synthesis of terminally arylated products in only two steps from linear alkanes. The current two-step C–H functionalization method is cost-effective, chemoselective, and occurs under mild conditions at a reasonable catalyst loading.

Acknowledgements

This research was supported financially by the Agence National de la Recherche (ANR-14-CE06-0001), the China Scholarship Council, the Swiss National Science Foundation (200021_165987), and the University of Basel. We thank Dr. Mouâd Alami, Dr. Grégory Danoun, Prof. Dr. Andreas Pfaltz, and Prof. Dr. Thomas Ward for helpful suggestions and comments, and Dr. Daniel Häussinger for assistance with NMR experiments.

Keywords: alkyl bromides · C–C coupling · homogeneous catalysis · palladium · remote functionalization

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 14793 – 14797
Angew. Chem. **2016**, *128*, 15013 – 15017

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Received: August 31, 2016