Remote Functionalization Hot Paper

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Air-Stable Pd^{I} Dimer Enabled Remote Functionalization: Access to Fluorinated 1,1-Diaryl Alkanes with Unprecedented Speed

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Abstract: *While remote functionalization via chain walking has the potential to enable access to molecules via novel disconnections, such processes require relatively long reaction times and can be in need of elevated temperatures. This work features a remote arylation in less than 10 min reaction time at room temperature over a distance of up to 11 carbons. The unprecedented speed is enabled by the air-stable Pd^{I} dimer $[Pd(\mu\text{-}I)(PCy_2{}^tBu)]_2$, which in contrast to its P^tBu_3 counterpart does not trigger direct coupling at the initiation site, but regioconvergent and chemoselective remote functionalization to yield valuable fluorinated 1,1-diaryl alkanes. Our combined experimental and computational studies rationalize the origins of switchability, which are primarily due to differences in dispersion interactions.*

The area of remote functionalization has seen a significant growth in recent years[1] owing to its potential to enable structural access from diverse building blocks, especially in cases where the more established direct cross-coupling reactions are less amenable. This concept predominantly capitalizes on iterative β-hydride elimination/reinsertion steps,[2] which translocate a metal catalyst along a carbon chain (via so-called "chain walking") and can be initiated through, for example, hydrofunctionalization of a remote olefin or migratory cross-coupling (see Figure 1 A). While there has been impressive progress in recent years in this context,[1,3] the current methodological repertoire to access 1,1-diaryl alkanes via such a remote functionalization strategy[4] requires relatively long reaction times (12–48 hours) and is limited in the substitution pattern; the vast majority of methods do not showcase the compatibility with *ortho*-substituents in these 1,1-diaryl alkanes.[5] In this context Baudoin recently reported a notable advance which relied on Pd-catalysis and could tolerate *ortho*-substituents, albeit requiring high temperatures (120 °C) during 48 hours and a terminal blocking group in the substrate to prevent alternative products (see Figure 1 B).[6,7]

Ortho-fluorinated 1,1-diaryl alkane motifs were not showcased. These motifs are of distinct importance, being featured in numerous bioactive compounds[8] with anti-HIV, anti-fungal or anti-blood clotting activities, for example. More generally, the presence of fluorine often enhances metabolic

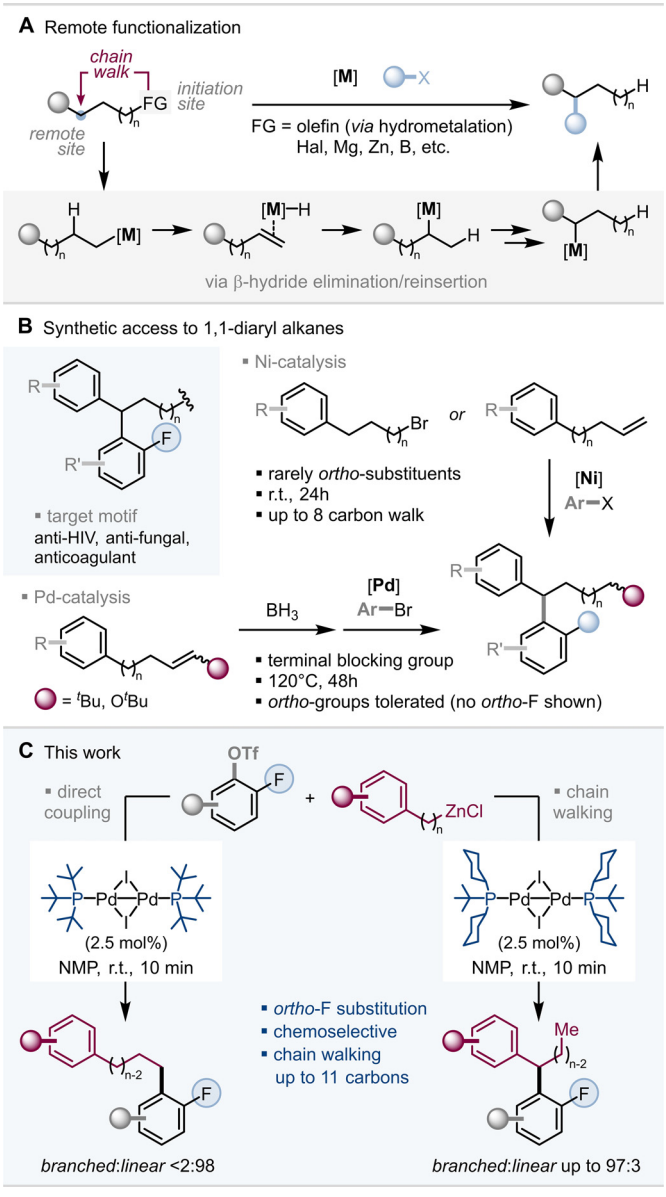

Figure 1. Remote functionalization, synthetic access to 1,1-diarylalkanes and this work.

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stability, solubility as well as lipophilicity properties of organic molecules.[9] However, the construction of *ortho*-fluorinated 1,1-diaryl alkanes via direct coupling approaches suffers either from the instability of *ortho*-fluorinated nucleophilic organometallic coupling partners, or in the alternative disconnection of benzylic substitution, from substrate dependence and functional group intolerance.[10]

The development of a remote functionalization approach to construct such *ortho*-fluorinated motifs in a rapid and modular fashion could therefore be greatly enabling.

We initially set out to test the reported chain walking methodology for the synthesis of 1,1-diaryl alkane substrates, which previously had reported selected examples with *ortho*-substituents[5] to see if fluorine could potentially be tolerated. When we employed *ortho*-fluorinated aryl halides along with phenyl alkyl bromides or phenyl alkenes, we observed incomplete walks resulting in mixtures of isomers. Additionally, when there was steric hindrance present in the arene to which the walk occurred (e.g. *o*-Me or *o*-*i*Pr arylalkyls), none of the desired 1,1-diaryl alkane product was obtained.[11]

With the goal to overcome these limitations and enable a modular access to *ortho*-fluorinated 1,1-diaryl alkanes, as well as push the boundaries of speed in the field of remote functionalization more generally, we set out to explore the reactivity of dinuclear Pd^{I} complexes in such migratory coupling reactions.

In our previous research, we could show that the air-stable and robust iodide-bridged Pd^{I} dimer $[Pd(\mu\text{-}I)(P^{t}Bu_3)]_2$ enables the site-selective alkylation of poly(pseudo)halogenated arenes within minutes, using alkyl zinc reagents as nucleophilic coupling partners.[12] The selectivity and speed were independent of the electronic and steric features exerted by the substrates, tolerating *ortho*-substituents as large as adamantyl,[12c] which contrasted typical Pd^{0}-based strategies that generally lack this substrate-independence. In light of the generality and speed, we wondered whether these features could be transferred to the chain-walking concept, that is, in a migratory cross-coupling approach with a modified Pd^{I} dimer.

We recently reported that the air-stable Pd^{I} dimer $[Pd(\mu\text{-}I)(PCy_2{}^{t}Bu)]_2$ enables *E*-selective olefin migration as well as C–C bond formations.[13] Since remote functionalization often proceeds via migration of a double bond along a carbon chain, we wondered if this dimer $[Pd(\mu\text{-}I)(PCy_2{}^{t}Bu)]_2$ could enable such a transformation (Figure 1C).

To test our hypothesis, we added phenylpropyl-ZnCl along with Pd^{I} dimer $[Pd(\mu\text{-}I)(PCy_2{}^{t}Bu)]_2$ to a solution of 3-chloro-2-fluorophenyl triflate in NMP. To our delight, we achieved regio- and chemoselective remote coupling at the OTf site within 10 minutes at room temperature to give **1** in excellent branched to linear selectivity (94:6) and 91% isolated yield of the branched product (Figure 2).

To the best of our knowledge, this reaction speed paired with selectivity is completely unprecedented. By contrast, using the $P^{t}Bu_3$-derived dimer instead, that is, $[Pd(\mu\text{-}I)(P^{t}Bu_3)]_2$, we obtained direct coupling to the linear product **26** in the same speed, without any migration, in line with our previous research (Figure 3A).[12e] As such, a subtle ligand modification within the Pd^{I} dimer framework can fully switch the reaction outcome towards the branched product, while retaining the beneficial features of air-stability and reaction speed.

We next set out to explore the generality of this transformation (Figure 2). In this context, we primarily focused on *ortho*-fluoro aryl triflate substrates that contained also C-Cl sites to create additional possibilities for downstream diversification. In all cases coupling was exclusively observed at the C-OTf site; the competing C-Cl site remained untouched.[16]

Variation of the alkyl zinc reagents in terms of chain length had no impact on the transformation; irrespective of chain length we achieved good yields and high regioselectivities within 10 minutes at room temperature. Electronic variations of the aryl group of the coupling partner are well tolerated, ranging from electron donating *tert*-butyl (**9**) to electron withdrawing trifluoromethyl-substituted aryl moieties (**4**, **10**). Notably, the *ortho*-methyl and -isopropyl groups (**6**, **7**) did not affect the reaction speed and efficiency, and only minimally effected the product selectivity (branched vs. linear). While as large substituents as isopropyl have so far not been showcased, the smaller *ortho*-methyl substituent (as in **6**) could otherwise only be tolerated under much harsher conditions, such as Baudoin's recent protocol,[6] requiring 120 °C and 48 h reaction time or Zhu's protocol,[5c] needing 80 °C for 24 h. Potentially coordinating functionalities such as the cyano group (**13**) did not impede the reaction. Heterocycles (**10**, **18** and **20**) were also equally effective.

Notably, the presence of a methyl group along the chain did not markedly impede the walk (**24**). Although a slightly lower branched to linear ratio was obtained, the branched product could be isolated in a good yield of 65% as a 1:1 mixture of diastereomers (Figure 3A).

Finally, to test the applicability of our method for secondary rather than primary alkyl zinc reagents, we employed an equal mixture of primary and secondary alkyl zinc bromide as a starting material (Figure 3A). The reaction proceeded with high selectivity (95:5) and gave the branched 1,1-diaryl product **25** in high yield (88%).

Intrigued by the unprecedented speed and high regioselectivity, we subsequently turned to computational studies to gain insight. We previously reviewed that depending on the precise reaction conditions as well as bridging halide of the Pd^{I} dimer, different active catalytic species can result, ranging from direct reactivity of the Pd^{I} dimer to being a precursor for Pd^{0} or Pd^{II}-H species.[17] Our previous studies concluded that under the herein employed conditions (i.e. organometallic coupling partner in NMP), the reactivity (and selectivity) for the $C(sp^2)$-OTf oxidative addition is consistent with a Pd^{0} species, either an anionic Pd ate complex or solvent coordinated (sol)$Pd^{0}L$.[12e,18] Following oxidative addition, a monophosphine Pd^{II} intermediate **I** will result (see Figure 3B). After transmetalation, reductive elimination to the linear product can potentially occur from the resulting intermediate **II** or β-H elimination can initiate the chain walk. Our calculations[19] at the SMD (DMAc) M06-2X-D3/def2-TZVP//MN15-D3(BJ)/def2-SVP level of theory[15] of the coupling of *ortho*-fluoro-*para*-chlorophenyl triflate with phenylpropyl-ZnCl indicate that while the reductive elimination towards the linear product is clearly favored for the $P^{t}Bu_3$

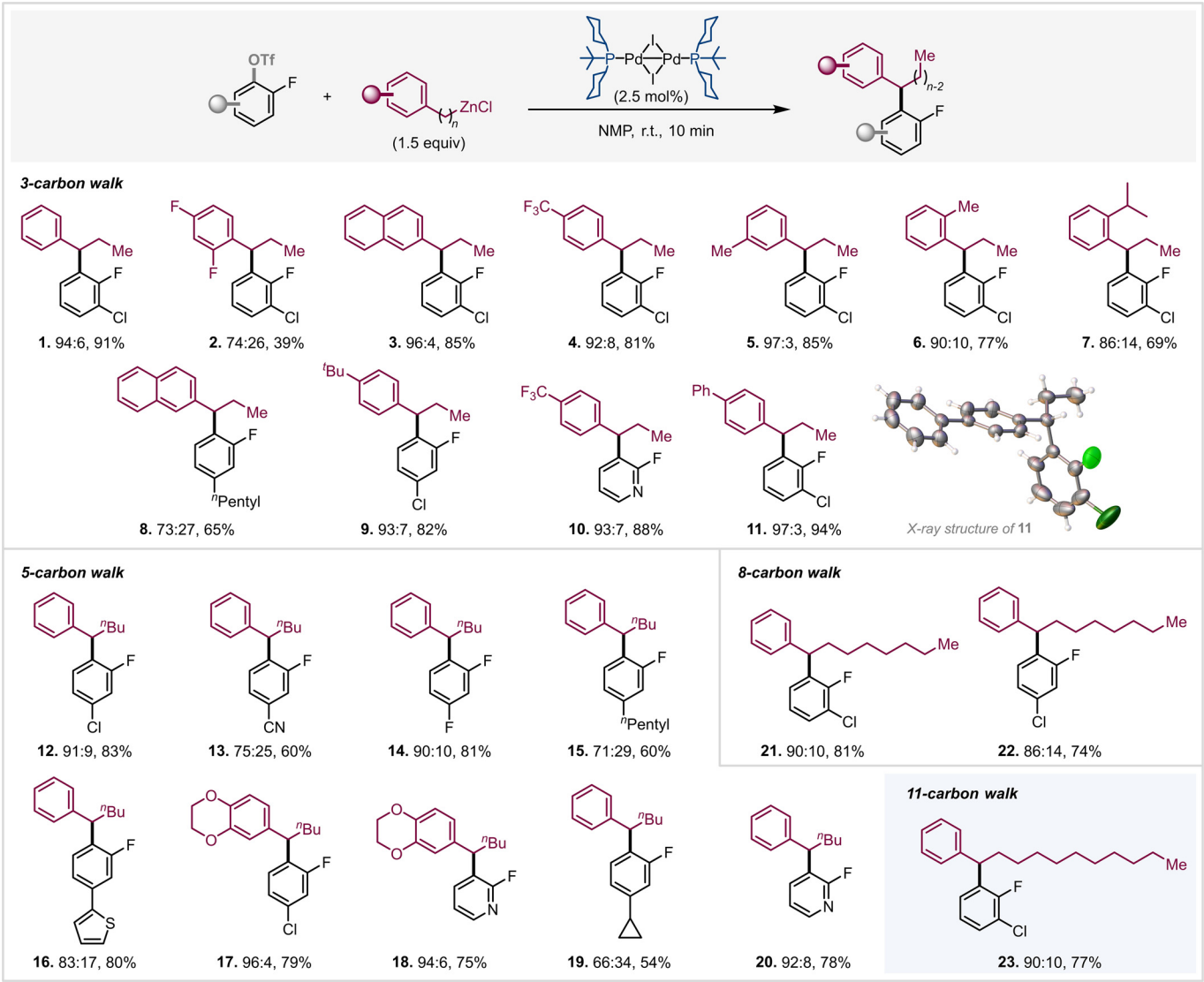

Figure 2. Scope of remote arylation. Reaction conditions: aryl triflate (0.2 mmol), $[Pd(\mu\text{-}I)(PCy_2{}^tBu)]_2$ (0.005 mmol, 2.5 mol%), organozinc reagent (0.24 mmol, 1.2 equiv, in THF) in NMP (1.5 mL) for 10 min at r.t. under argon. Ratios of branched to linear product and isolated yields of branched products are given.[11,14]

ligand (by $\Delta\Delta G^{\ddagger} = 1.8$ kcal mol^{-1}), in the case of the $PCy_2{}^tBu$ ligand, the competing β-hydride elimination is favored (by $\Delta\Delta G^{\ddagger} = 1.2$ kcal mol^{-1}), which is consistent with the observed product divergence. The subsequent chain walk via consecutive β-hydride elimination and reinsertion steps (see Figure 3C) is also of lower activation free energy barrier than the reductive elimination towards the linear product.[11] The lowest transition state for an irreversible reductive elimination from a Pd^{II}-alkyl intermediate along the walk likely determines the product selectivity. Comparing the three possible reductive elimination transition states showed that indeed formation of branched 1,1-diaryl is favored over the linear analogues by $\Delta\Delta G^{\ddagger} = 2.6$ ($TS_{RE,C1}$ vs. $TS_{RE,C2}$) and 3.8 ($TS_{RE,C1}$ vs. $TS_{RE,C3}$) kcal mol^{-1}, respectively.[11]

As such, the calculations are fully consistent with the observed product selectivities. To gain greater insight on the origins of the subtle ligand impacts, we performed a distortion/interaction analysis[20] of the reductive elimination and β-hydride elimination transition states (see supporting information for details). Our analysis indicated that while there was no marked difference in the fragment energies for the two ligands in the reductive elimination, there is a difference in interaction energies in the β-H elimination transition state. For $PCy_2{}^tBu$ we determined a 4.2 kcal mol^{-1} greater interaction energy compared to P^tBu_3. Our further analysis of the underlying non-covalent interactions (NCI analysis) indicated that the primary origin of this increased interaction energy is dispersion. With other words, the chain walking is favored for $PCy_2{}^tBu$ as a consequence of enhanced stabilizing dispersion forces.

Aside from the product selectivity, the overall reaction speed of only 10 min at room temperature is unprecedented also (as compared to 24 h reaction times in Ni-based couplings or 48 h in Pd-based protocols).[4–6] Since the chain walking relies on the analogous elementary steps as other Pd-based protocols (i.e. Pd^{II} β-H elimination and reinsertion, see

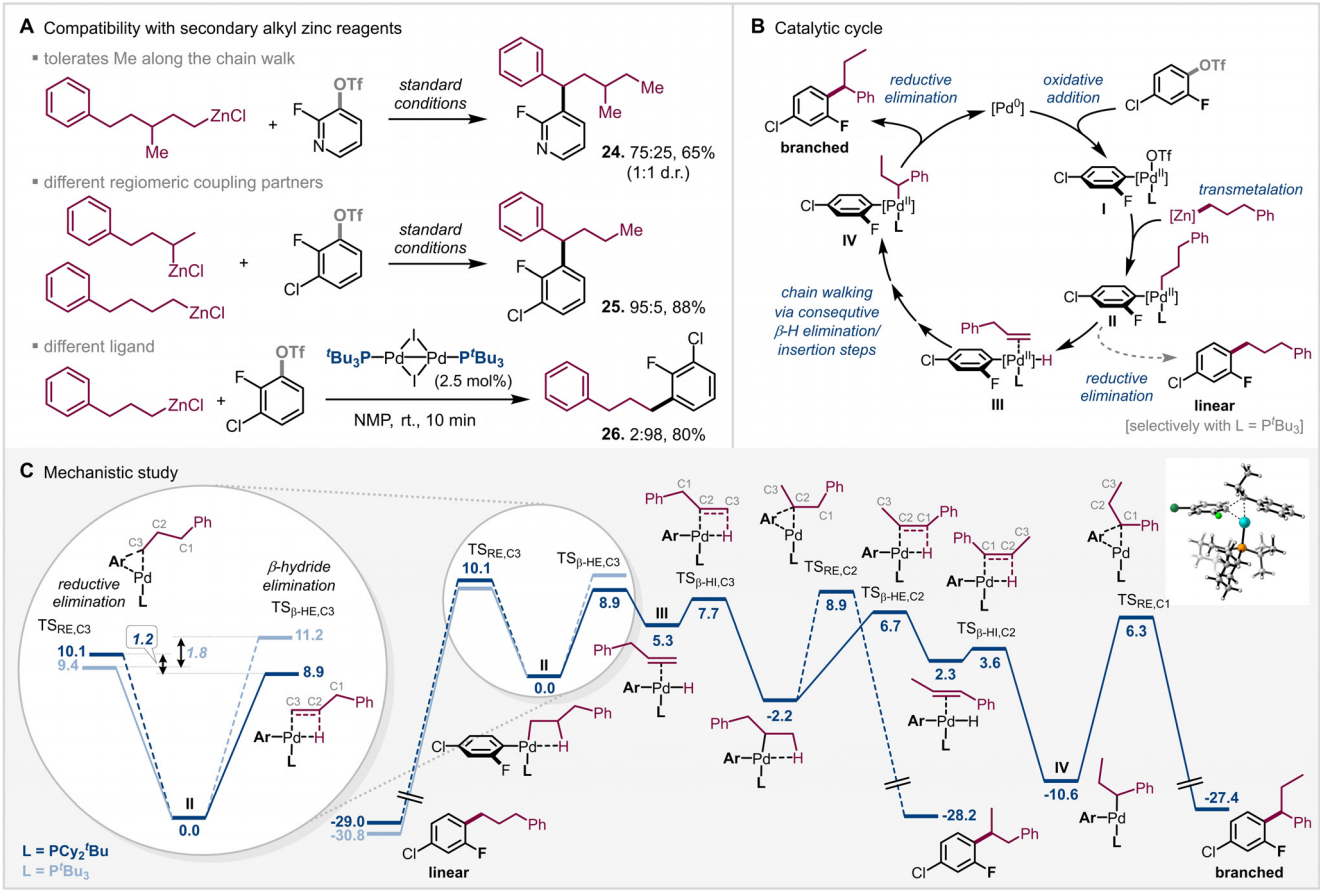

Figure 3. a) Compatibility of the method with secondary alkyl zinc reagents; b) Catalytic cycle; c) Mechanistic study. Energies (in kcal mol^{-1}) refer to Gibbs free energies relative to Pd^{II} obtained after transmetalation, calculated at the SMD (DMAc) M06-2X-D3/def2-TZVP//MN15-D3(BJ)/def2-SVP level of theory.[11,15]

Figure 3A), the unprecedented overall speed implies that the pre-catalyst and its speciation in solution, does not only influence the release of the active catalytic Pd^0 species, but also its fate and availability in later catalytic turnover. The dynamic interplay of the various components (speciation) in solution clearly effects the entire transformation, which is an observation that has not been the focus in homogenous catalysis so far. With the Pd^I dimer entity being rapidly and nucleophilically activated[17,21] to the monophosphine Pd^0 species without dynamic association/dissociation events of competing phosphine ligands (which frequently is the case in Pd^0 based protocols that rely on initial ligand dissociation steps), the individual elementary steps as well as later catalyst turnover also appear to be unaffected by competing events in the Pd^I dimer protocol. These results suggest that the nature of the pre-catalyst and overall reservoir of active species should therefore shift into greater focus and be considered more closely in the future development of remote functionalization strategies.

In conclusion, we have demonstrated a chemo- and regioselective remote functionalization strategy for the modular access to *ortho*-fluorinated 1,1-diaryl alkanes. The process is enabled by an air-stable Pd^I dimer and couples alkyl organozinc reagents with aryl triflates that possess *ortho*-fluoro substituents as well as competing C-Cl sites. The migratory cross-coupling proceeds with unprecedented speed in only 10 min at room temperature for up to 11 carbon chains and is tolerant of various functionalities and substitution patterns that are not accessible with alternative chain-walking protocols. Our computational investigation indicates that facile β-hydride elimination and reinsertion steps allow for a rapid chain walking, which is primarily a consequence of greater dispersive interaction with PCy$_2$^{t}Bu, and the low barrier for the reductive elimination step is the origin of selectivity for the formation of benzylic branched product. More generally, the crucial role of the reservoir of the active catalytic species on the overall reaction speed and efficiency is showcased, an aspect that has so far not been a focus in the area of remote functionalization.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalysis · dinuclear Pd^{I} · remote functionalization · selectivity

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