Atom Transfer

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Palladium-Catalyzed Intramolecular Iodine-Transfer Reactions in the Presence of β-Hydrogen Atoms**

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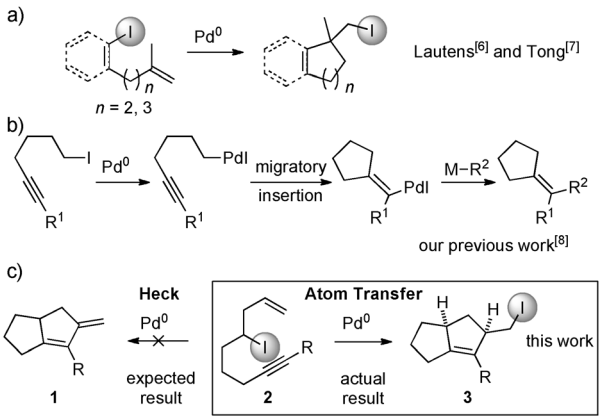
The ideal chemical transformation is one where all atoms in the starting materials are present in the product with all other reagents used catalytically.[1] Atom-economical reactions strive to achieve this ideal and are essential for the continued maturation of organic chemistry and the mitigation of its negative effects on the environment.[2] The search for atom-economical processes has advanced the field of catalysis and broadened the study of environmental chemistry. The impressive industrial synthesis of sitagliptin highlights the importance of atom economy in the chemical industry.[3] Therefore, the identification of reactions that achieve high atom economy is a worthwhile endeavor.

Palladium-catalyzed transformations are one of the most important carbon–carbon bond forming reactions in medicinal chemistry[4] and total synthesis.[5] Recent interest in palladium-catalyzed atom-transfer reactions has grown from the work of Lautens et al.[6] and Tong et al.[7] They have demonstrated the ability of aryl, vinyl, and alkynyl halides to undergo intra- and intermolecular insertion events and subsequently reductive elimination to form alkyl iodides in the absence of β-hydrogen atoms (Scheme 1a). A useful extension of this atom-transfer chemistry would be the application of alkyl halides and olefin insertion in the presence of β-hydrogen atoms.

We recently reported a tandem alkyne insertion/Suzuki reaction of primary iodides (Scheme 1b).[8] Since a secondary iodide also worked in the alkyne insertion/Suzuki reaction, we sought to extend this methodology to a tandem alkyne insertion/Heck reaction to produce bicyclic *exo* olefin products of type **1** (Scheme 1c). However, preliminary reactions did not yield Heck products **1**, but rather the iodine-transfer product **3**. The unexpected formation of the diquinane **3**



Scheme 1. a) Previous palladium-catalyzed iodine-transfer reactions in the absence of β-hydrogen atoms. b) Tandem insertion/Suzuki reaction of primary iodides. c) An attempted alkyne insertion/Heck reaction leads to a facile palladium-catalyzed iodine-transfer reaction in the presence of β-hydrogen atoms.

bearing a primary iodide in high yield with few side products was deemed worthy of investigation, especially given the need to develop direct syntheses of complex compounds containing tetrasubstituted olefins.[9] The transformation allows the use of easy-to-access compounds of type **2** (two to three steps from commercial materials) for the synthesis of functionalized diquinanes, which are important structural motifs found in numerous natural products,[10] and provides substitution patterns complementary to the current state-of-the-art approach, the Pauson–Khand reaction.[11] Consequently, we set out to determine the scope and reactivity of this important iodine-transfer reaction.

The palladium-catalyzed iodine-transfer reaction was optimized through the systematic evaluation of all relevant reaction parameters. Interestingly, the addition of base was essential to achieve full conversion. Without the inclusion of base, the catalyst did not turn over and precipitated as $[Pd(PPh_3)_2I_2]$, thereby suggesting a role for the base in the reduction of Pd^{II} species. Interestingly, the addition of super-stoichiometric amounts of iodine (sodium iodide or tetrabutylammonium iodide) relative to palladium shut down the reaction completely and allowed for the quantitative recovery of starting material.

Utilizing optimal reaction conditions (Cs_2CO_3, $[Pd(PPh_3)_4]$, PhMe, 50 °C, 20 h), a variety of substrates were evaluated (Table 1). The iodine-transfer reaction proved general, providing *cis* bicyclic ring systems with moderate-to-good d.r. values. Varying the electronic properties of the internal alkyne with electron-rich and electron-deficient

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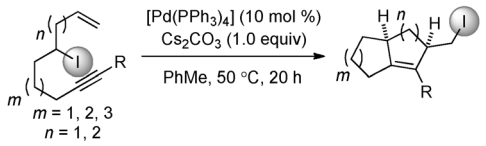
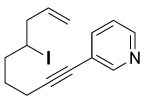
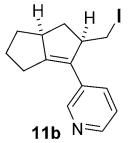
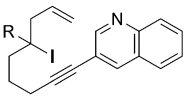
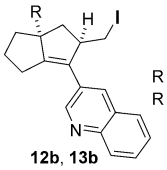
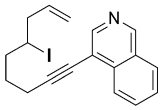
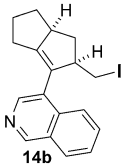
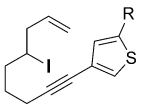
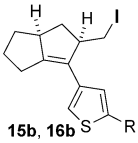
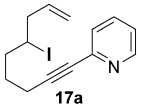
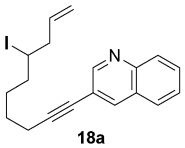
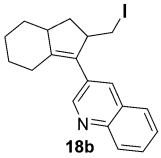
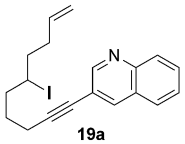
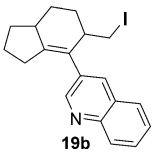
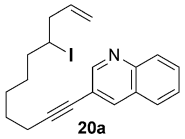
Table 1: Atom transfer substrate scope.



Entry	Substrate	Product	Yield [%]	d.r.
1	R = 4-MeOC$_6$H$_4$		87	14:1
2	= 3,4,5-(MeO)$_3$C$_6$H$_2$		86	7:1
3	= 2-CO$_2$MeC$_6$H$_4$		65	6:1
4	= 4-CO$_2$MeC$_6$H$_4$		73	12:1
5	= H		NR	N/A
6	= CHCH$_2$	**4a–10a**	**4b–10b** 64	7:1
7	= C$_4$H$_9$		71[a]	> 20:1
8	 **11a**	 **11b**	88	10:1
9		 R = H	82	14:1
10	**12a**, **13a**	**12b**, **13b** R = CH$_3$	55	>20:1
11	 **14a**	 **14b**	68	> 20:1
12		 R = H	72	5:1
13	**15a**, **16a**	**15b**, **16b** R = CHO	81	> 20:1
14	 **17a**	–	NR	N/A
15	 **18a**	 **18b**	63[b,c]	ND
16	 **19a**	 **19b**	71[b,c]	ND
17	 **20a**	–	0[d]	N/A

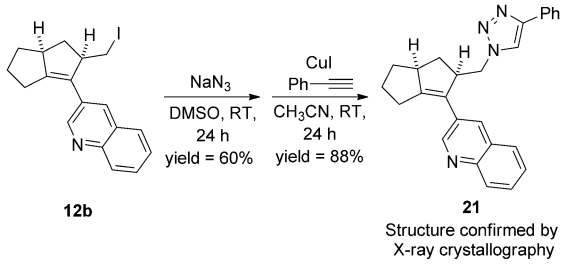
[a] Reaction performed at 60 °C. [b] Standard conditions lead to NR (recovered starting material). [c] 80 °C, $NaHCO_3$ (1.0 equiv). [d] 140 °C, $NaHCO_3$ (1.0 equiv) leads to starting material decomposition. NR = no reaction, ND = not determined, N/A = not available.

aromatic groups had little effect on the reaction, providing good yields of primary iodides **4b**, **5b**, **6b**, and **7b** (entries 1–4, Table 1). Alkynes substituted with either an alkyl or vinyl group proceeded cleanly in satisfactory yields, generating diene **9b** and all-alkyl tetrasubstituted olefin **10b**, respectively (entries 6 and 7, Table 1). Additionally, tertiary iodide **13a** provided iodine-transfer product **13b** in 55 % yield as a single diastereomer as determined by ^{1}H NMR analysis (entry 10, Table 1). The reaction tolerated a variety of heterocycles, allowing the formation of primary iodides in the presence of pyridine, quinoline, isoquinoline, and thiofuran (entries 8–13, 15, and 16, Table 1). Functional groups such as ethers, esters, and aldehydes were also compatible with the reaction conditions (entries 1–4 and 13, Table 1). Unfortunately, substrates capable of palladium sequestration, such as terminal alkyne **8a** and 2-pyridine **17a**, suffered from a lack of reactivity (entries 5 and 14, Table 1).

While the reaction conditions worked well for the formation of diquinane ring systems, attempts to access hydroindene ring systems **18b** and **19b** led to the recovery of starting material under standard reaction conditions (entries 15 and 16, Table 1). Higher reaction temperatures (e.g., 80 °C) effected the cyclization but produced formal Heck products of type **1**, presumably through E_2 elimination by Cs_2CO_3 of **18b** and **19b** (see the Supporting Information). Substitution of Cs_2CO_3 with a weaker base, $NaHCO_3$, allowed for the isolation of the primary iodides **18b** and **19b** in 63 % and 71 % yield, respectively (entries 15 and 16, Table 1). Even under elevated temperatures (140 °C), all attempts to cyclize secondary iodide **20a** failed to produce the hydroazulene system, despite signficant consumption of starting material (entry 17, Table 1).

The primary iodide products can be elaborated into high-value, drug-like molecules through standard chemistry. For example, triazole **21** was synthesized in two steps and crystallized for unambiguous assignment of relative stereochemistry by using X-ray diffraction analysis (Scheme 2). The *cis* relative stereochemistry would be expected from the pseudo-equatorial orientation of the terminal olefin during the second insertion.

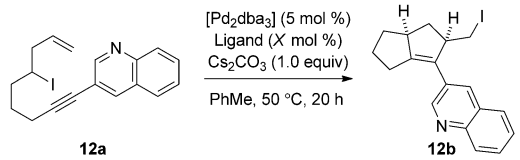
While the iodine-transfer reaction reported here may proceed through a radical mechanism, variation of the phosphine ligands revealed a clear influence on conversion (at 20 h) and d.r., thereby arguing against a purely free-radical mechanism (Table 2). For example, minor modifications to the PPh_3 ligand had significant effects. The addition of



12b **21**
Structure confirmed by X-ray crystallography

Scheme 2. Derivatization of primary iodide **12b** and confirmation of relative stereochemistry.[17]

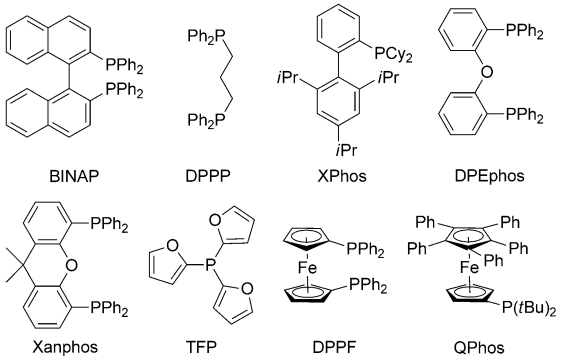
Table 2: The dependence of conversion and d.r. on the ligand.



12a **12b**

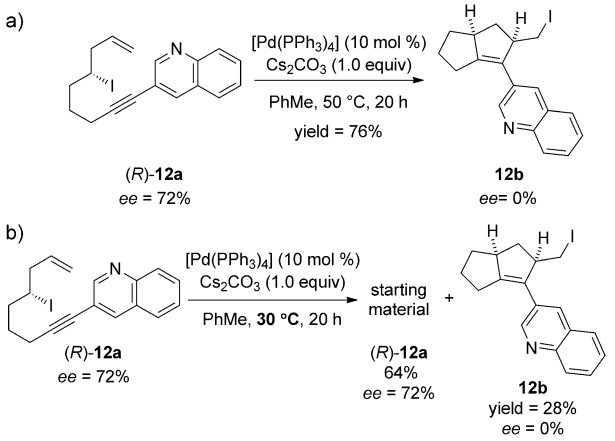
Entry	Ligand	*X*	Conversion [%]	d.r.
1	PPh_3	10	0	N/A
2	PPh_3	20	29	N/A
3	PPh_3	30	53	N/A
4	PPh_3	40	95	13:1
5	PPh_3[a]	40	100	14:1
6	$P(4\text{-}CF_3C_6H_4)_3$	40	33	13:1
7	$P(4\text{-}OMeC_6H_4)_3$	40	100	10:1
8	*rac*-BINAP	20	80	>30:1[b]
9	XPhos	40	66	>20:1
10	QPhos	20	13	N/A
11	DPEphos	20	7	N/A
12	DPPP	20	9	N/A
13	TFP	40	4	N/A
14	$P(2\text{-}MeC_6H_4)_3$	40	0	–
15	$AsPh_3$	40	0	–
16	DPPF	20	0	–
17	Xanphos	20	0	–
18	–	–	0	–

[a] $[Pd(PPh_3)_4]$ (10 mol%). [b] See the Supporting Information.



a *para*-methoxy group afforded faster reactions with lower d.r. value (entry 7, Table 2), whereas a *para*-trifluoromethyl group produced slower reactions with virtually unchanged d.r. value (entry 6, Table 2). The sterically encumbered monodentate phosphines XPhos and QPhos, which have been used successfully in previous atom-transfer reactions,[6] proved inferior to PPh_3 in terms of conversion (entries 9 and 10, Table 2). Note that the reactions described in entries 6, 8, and 9 all reached full conversion at later time points. More electron-donating phosphines, such as $P(tBu)_3$, $P(Cy)_3$, and $MeP(tBu)_2$, led to complex reaction mixtures with no observable product (data not shown). Weakly coordinating ligands such as TFP or $AsPh_3$ were ineffective for the reaction (entries 13 and 15, Table 2). Although *rac*-BINAP provided reasonable conversion with high d.r. value (entry 8, Table 2), the other bidentate phosphines tested proved ineffective (entries 11, 12, 16, and 17, Table 2). Furthermore, the use of (*S*)-BINAP provided racemic product, unlike in previous examples of palladium-catalyzed atom-transfer reactions.[7a] Finally, in the absence of any phosphine no reaction was observed (entry 18, Table 2).

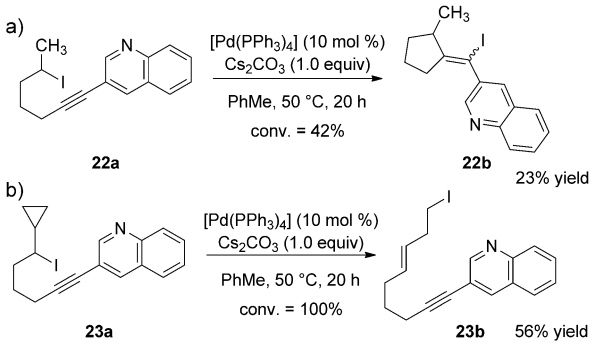
Oxidative addition of alkyl halides by palladium(0) most commonly proceeds through either S_N2[12] or radical mechanisms.[13] To probe the nature of oxidative addition, enantioenriched secondary iodide (*R*)-**12a** was prepared and subjected to standard reaction conditions (Scheme 3a). The



Scheme 3. a) Racemization of enantioenriched substrate (*R*)-**12a**; b) recovery of enantioenriched substrate (*R*)-**12a** at low conversion.

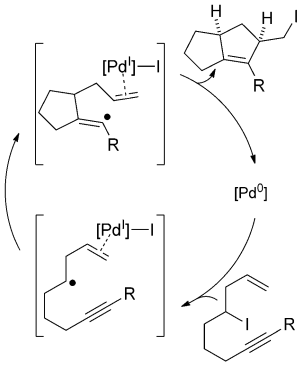
isolation of racemic **12b** rules out an S_N2 pathway for oxidative addition. To test whether reversible, two-electron oxidative addition is the source of racemization, enantioenriched secondary iodide (*R*)-**12a** (72% *ee*) was subjected to the optimized reaction conditions at 30°C (Scheme 3b). The reaction produced low conversion at 20 h with 28% yield of the racemic product **12b** and 64% recovered starting material (*R*)-**12a** without any observable erosion of *ee*. These results strongly suggest that a poorly stereoselective, reversible, two-electron oxidative addition is not responsible for the formation of racemic product.

Attempts to intercept any carbopalladium species in the catalytic cycle with $PhB(OH)_2$ under the optimized reaction conditions were unsuccessful, returning only secondary iodide starting material **12a**. TEMPO (2,2,6,6-tetramethylpiperdine 1-oxyl)[13a,14] and galvinoxyl[15] are often used as radical traps in free-radical chemistry. Conducting the reaction in the presence of one equivalent of TEMPO or galvinoxyl led to no reaction and quantitative recovery of starting material, an outcome opposite to the primary iodides studied previously.[8] Furthermore, the terminal olefin proved critical for the overall efficiency of the transformation. For example, when the allyl group was replaced with a methyl group, the reaction produced vinyl iodide **22b** in low yield with multiple reduction products (42% conversion, 23% yield of *E*/*Z* mixture, Scheme 4a). While products expected from a cyclopropylcarbinyl rearrangement were not observed for any of the substrates in Table 2, replacing the terminal olefin with a cyclopropyl ring provided ring-opened primary iodide **23b** (Scheme 4b). Since radical atom-transfer cyclizations are known,[16] we subjected substrate **12a** to a range of radical conditions (see the Supporting Information). Under most



Scheme 4. a) Removing the terminal olefin severely compromises the efficiency of the iodine-transfer reaction; b) cyclopropylcarbinyl rearrangement leads to no reaction with the internal alkyne.

conditions, quantitative recovery of starting material was observed. The iodine-transfer product could be observed in low yield using conditions reported by Curran et al. (slow addition of azobisisobutyronitrile (AIBN) and nBu$_3$SnH in benzene, 85 °C, 24 h).[16d] The results from the free-radical experiments (see the Supporting Information) clearly demonstrate the superiority of this method over traditional free-radical methods. Taken together, the racemic product, ligand influence on d.r., and compromised reactivity in the absence of the terminal olefin suggest a role for palladium beyond radical initiation. A possible explanation for these observations would be the coordination of a putative Pd^{I} intermediate to the terminal olefin (Scheme 5).



Scheme 5. Possible mechanistic rationale for the role of the palladium.

In summary, we have developed an iodine-transfer reaction for the formation of primary iodides from acyclic secondary iodides with concomitant creation of a bicyclic ring. Notably, this transformation also delivers stereo- and regiodefined tetrasubstituted olefins. The ability to utilize alkyl iodides and terminate the reaction in the presence of β-hydrogen atoms provides complementary reactivity to that which has already been developed by Lautens et al.[6] and Tong et al.[7] The reaction enjoys wide functional group tolerance, including a range of heterocycles, and can be used in the construction of difficult-to-access diquinane and hydroindene ring systems. Preliminary mechanistic studies rule out an S_N2 oxidative addition. Additionally, phosphine ligands have a direct impact on the conversion and d.r. of the reaction, thereby arguing against a purely free-radical reaction. Further efforts will be directed towards a greater understanding of reaction mechanism and expanding the scope of this interesting transformation.

Experimental Section

General procedure for the atom transfer reaction:

An oven-dried Kimberly-Chase 8 mL screw thread culture tube was purged with nitrogen, then charged with [Pd(PPh$_3$)$_4$] (0.10 equiv) and Cs_2CO_3 (1.0 equiv). The flask was then purged with nitrogen. A solution of the alkyl iodide (1.0 equiv) in PhMe (0.10 M) was then added all at once by using a gas-tight syringe, and the tube was sealed with the screw top vial. The reaction was stirred for 20 h at 50 °C. The reaction was returned to room temperature, quenched with a 10% aqueous solution of *N*-acyl cysteine (5 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were then washed with H_2O (25 mL), dried ($MgSO_4$), filtered, and concentrated to give a residue. The residue was purified by silica flash chromatography using hexanes and ethyl acetate in appropriate combination based on the R_f value of the desired product.

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[17] CCDC 963866 (**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

