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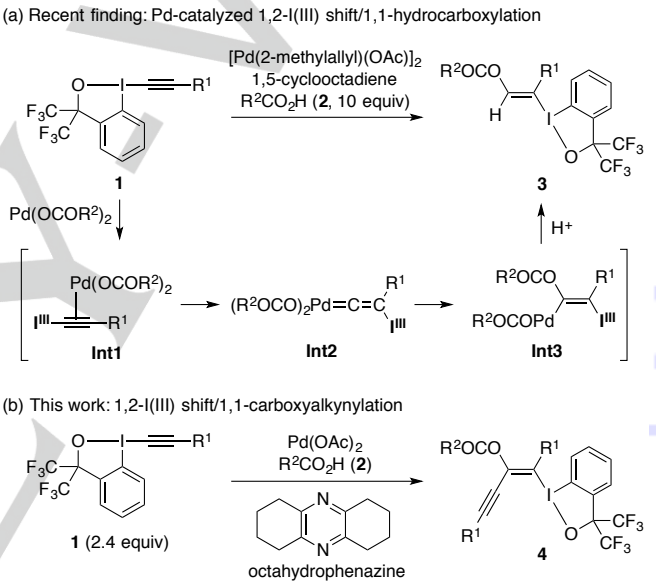
Pd-Catalyzed, Ligand-Enabled Stereoselective 1,2-Iodine(III) Shift/1,1-Carboxyalkynylation of Alkynylbenziodoxoles**

Junliang Wu, Kai Xu, Hajime Hirao,* and Naohiko Yoshikai*[a]

Abstract: A palladium(II)-catalyzed 2:1 coupling reaction of alkynylbenziodoxole with carboxylic acid to afford (alk-1-en-3-ynyl)benziodoxole, which is efficiently promoted by an octahydrophenazine ligand, is reported. The reaction involves palladium-assisted 1,2-iodine(III) shift of the alkynylbenziodoxole followed by stereoselective introduction of carboxy and alkynyl groups, the latter originating from another molecule of the alkynylbenziodoxole, into the 1-position of the transient Pd–vinylidene species. The product of this 1,1-carboxyalkynylation reaction serves as a novel functionalized enyne-type building block for further synthetic transformations.

As a part of extensive studies on the use of hypervalent iodine compounds in organic synthesis,[1] alkynyl-λ^3-iodanes have been established as reagents for electrophilic alkynyl group transfer to nucleophiles, offering an array of alkynylation methods complementary to the conventional alkynylation reactions involving nucleophilic acetylides.[1a-f,2] In particular, cyclic alkynyl-λ^3-iodanes such as alkynylbenziodoxol(on)es[1c-f,3] feature increased stability and have found a growing number of applications in non-conventional alkynylation reactions involving C–H bond functionalization,[4] decarboxylation,[5] or other mechanistically intriguing processes.[6]

While alkynylbenziodoxol(on)es have been primarily designed and explored as reagents for alkynylation, notable examples of their transformations beyond simple alkynyl group transfer have been reported, including furan-forming condensation by us,[7] oxy-alkynylation of diazo compounds by Waser,[8] and α-vinylidenation and α-vinylidenation/γ-alkynylation of aldehydes by Huang.[9] As one of such examples, we have recently disclosed a palladium-catalyzed reaction between alkynylbenziodoxole **1** and carboxylic acid **2** that proceeds via 1,2-iodine(III) shift/1,1-hydrocarboxylation processes, affording synthetically versatile β-oxyalkenylbenziodoxole **3** in a stereocontrolled manner (Scheme 1a).[7c,10] The reaction can be rationalized by a sequence of 1,2-shift of the benziodoxole moiety of Pd(II)-coordinated alkynylbenziodoxole (**Int1**),[11,12] migratory insertion of the transient vinylidene–Pd(II) species (**Int2**), and protonation of the resulting β-iodo(III)alkenyl–Pd(II) species (**Int3**). We hypothesized that interception of the putative intermediate **Int3** with an electrophile rather than a proton would lead to a tetrasubstituted alkenylbenziodoxole derivative. On the basis of this hypothesis, we have developed an efficient 2:1 coupling reaction between **1** and **2** to afford (alk-1-en-3-ynyl)benziodoxole **4**, which is enabled by a Pd(II)–octahydrophenazine catalyst (Scheme 1b). In this carboxylative dimerization, one molecule of **1** undergoes the 1,2-I(III) shift, while the other transfers the alkynyl group to the former in the stereoselective 1,1-carboxyalkynylation process. The product **4** serves as a functionalized enyne that is amenable to a series of further synthetic transformations.



Scheme 1. Pd-catalyzed 1,2-I(III) shift/1,1-carboxyfunctionalization of alkynylbenziodoxole.

Table 1 summarizes the screening process that led to the identification of octahydrophenazine as the optimum ligand for the present 1,1-carboxyalkynylation. Exposure of alkynylbenziodoxole **1a** (2.4 equiv) and benzoic acid (**2a**) to $Pd(OAc)_2$ alone (10 mol %) resulted in a complete decomposition of **1a** to a complex mixture of products, with an observation of the decomposition of the Pd(II) catalyst to Pd black (entry 1). The addition of pyridine (**L1**, 1 equiv) had a dramatic effect on the reaction outcome, affording the enyne product **4a** in 40% yield (entry 2).[13] In contrast, the use of a catalytic amount of pyridine (15 mol %) resulted in a predominance of the decomposition of **1a** and a diminished yield of **4a** (entry 3). The same trend was observed for a series of pyridine-based and related ligands, including 2,6-diethylpyridine (**L2**) and 2,3-diethylquinoxaline (**L3**) (entries 4–7). However, two effective ligands, tetrahydrophenazine (**L4**) and octahydrophenazine (**L5**), were identified upon further screening. **L4** afforded **4a** in good yields, with both stoichiometric and catalytic loading (entries 8 and 9). Conversely, the stoichiometric

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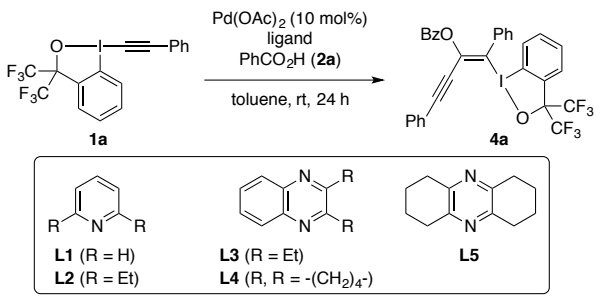
use of **L5** slowed the reaction, albeit under retention of an excellent mass balance (entry 10). Using a catalytic amount of **L5**, the reaction rate was restored and **4a** was obtained in almost quantitative yield (entry 11). Note that the hydrocarboxylation product (Scheme 1a) was not observed in these optimization experiments. On the other hand, the optimized catalytic system for the hydrocarboxylation only produced a mixture of the hydrocarboxylation and the carboxyalkynylation products when an excess amount of **1a** was used.

Table 1. Effect of reaction conditions on addition of N-H imine **1a** vinyltrimethylsilane.[a]

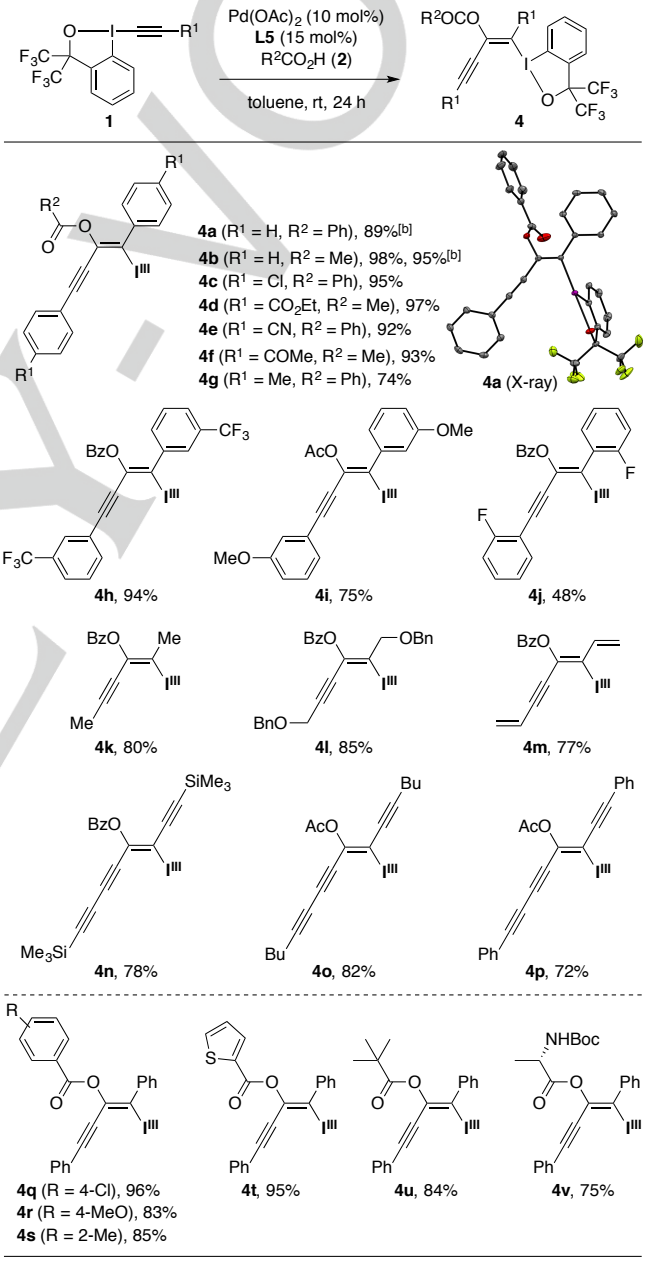


Entry	Ligand (mol%)	Conv. of **1a** [%]	Yield [%][b]
1	None	100	0
2	**L1** (100)	100	40
3	**L1** (15)	100	< 5
4	**L2** (100)	100	60
5	**L2** (15)	100	< 10
6	**L3** (100)	100	40
7	**L3** (15)	100	< 5
8	**L4** (100)	100	85
9	**L4** (15)	100	70
10	**L5** (100)	51	48
11	**L5** (15)	100	98 (95)

[a] Conditions: **1a** (0.24 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), ligand, toluene (0.067 M), room temperature, 24 h. [b] Determined by ^{19}F NMR spectroscopy using 1,4-bis(trifluoromethyl)benzene as an internal standard. Isolated yield shown in parentheses.

Having identified **L5** as the optimal ligand, we explored the scope of the 1,2-I(III) shift/1,1-carboxyalkynylation, which is summarized in Table 2. A variety of aryl(alkynyl)benziodoxoles, especially those bearing electron-withdrawing groups, reacted smoothly with **2a** or acetic acid (**2b**) to afford the desired (alk-1-en-3-ynyl)benziodoxoles **4a**–**4j** in moderate to excellent yields. In contrast, as was also the case with the 1,1-hydrocarboxylation,[7c] electron-rich 4-methoxyphenyl(ethynyl)benziodoxole decomposed under the applied conditions, not affording the desired product. The scalability of the present reaction was demonstrated by a gram-scale reaction of **1a** (2 mmol, 2.26 g) with **2a** or **2b**, which afforded **4a** or **4b**, respectively, without significant decrease in the yield. Benziodoxoles derived from alkylacetylenes, enynes, and diynes were also amenable to the 1,1-carboxyalkynylation, and afforded the desired alkenylbenziodoxole products including those containing novel oligoenyne moieties (**4m**–**4p**). Apart from benzoic acid and acetic acid, a series of aryl- and alkylcarboxylic acids could also be employed as reaction partners for **1a**, which afforded the corresponding 1,1-carboxyalkynylation products (**4q**–**4v**) in good to excellent yields (75–96%).

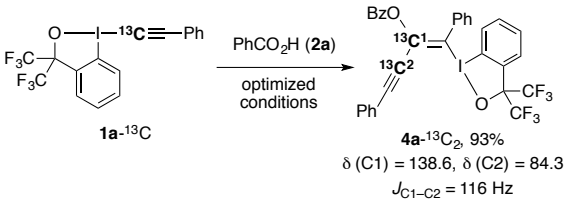
Table 2. Scope of 1,2-I(III) shift/1,1-carboxyalkynylation[a]



[a] The reaction was performed under the conditions in Table 1, entry 11. [b] 2 mmol scale with respect to **2**.

The reaction of ^{13}C-labeled alkynylbenziodoxole **1a**-^{13}C with **2a** under the present reaction conditions afforded the product **4a**-$^{13}C_2$, whose ^{13}C NMR spectrum confirmed the presence of

two adjacent ^{13}C atoms in the middle of the enyne chain with a large J_{C-C} coupling constant of 116 Hz (Scheme 2). This observation corroborates the notion of 1,2-I(III) shift and also demonstrates that the incorporation of the phenylethynyl group occurs without migration of the phenyl group.



Scheme 2. ^{13}C-Labeling experiment.

As previously done for the 1,1-hydrocarboxylation,[7c] the Pd(II)-assisted 1,2-I(III) shift and the subsequent vinylidene insertion into the Pd–carboxylate bond in the presence of **L5** were probed by density functional theory (DFT) calculations (Figure 1). $Pd(OAc)_2$, **L5**, and propynylbenziodoxole **1j** form a π-complex **Int1**. Though endergonic, **Int1** undergoes 1,2-I(III) shift via **TS1** with a relatively small activation energy of 8.4 kcal mol^{-1} to generate a vinylidene–Pd(II) species **Int2**. While **Int2** may easily revert back to **Int1** ($\Delta G^{\ddagger}$ = 1.7 kcal mol^{-1}), it can also undergo vinylidene insertion into the Pd–OAc moiety via a five-membered cyclic **TS2** ($\Delta G^{\ddagger}$ = 4.4 kcal mol^{-1}) to give a more stable β-iodo(III)alkenyl–Pd intermediate **Int3**. One of the distinct structural features of the present reaction pathway can be found in the "vinylidene" species **Int2**, where the I(III) center is almost equally distant from the α- and β-carbons (2.6–2.7 Å). Thus, **Int2** may also be regarded as an alkynyl–Pd species coordinated by a cationic I(III) moiety, as pointed out in Ariafard's computational study on related systems.[11,14]

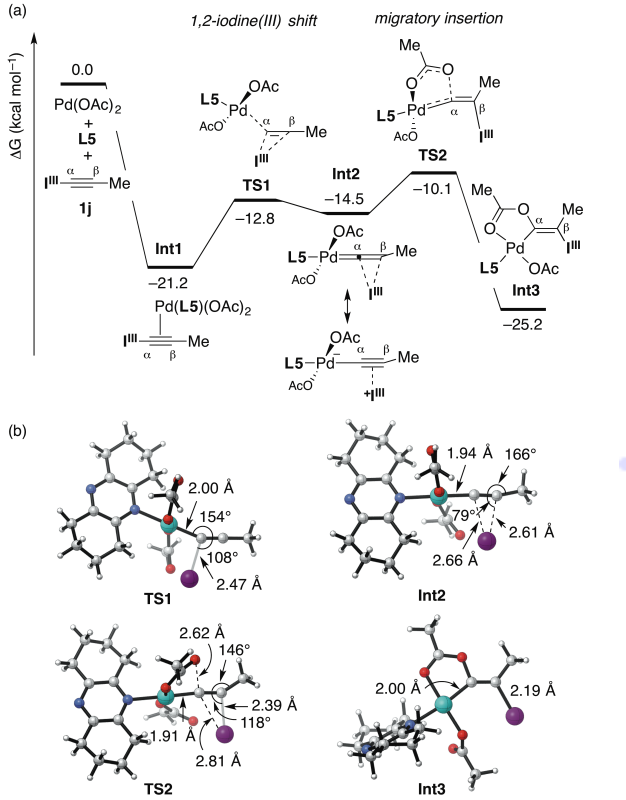
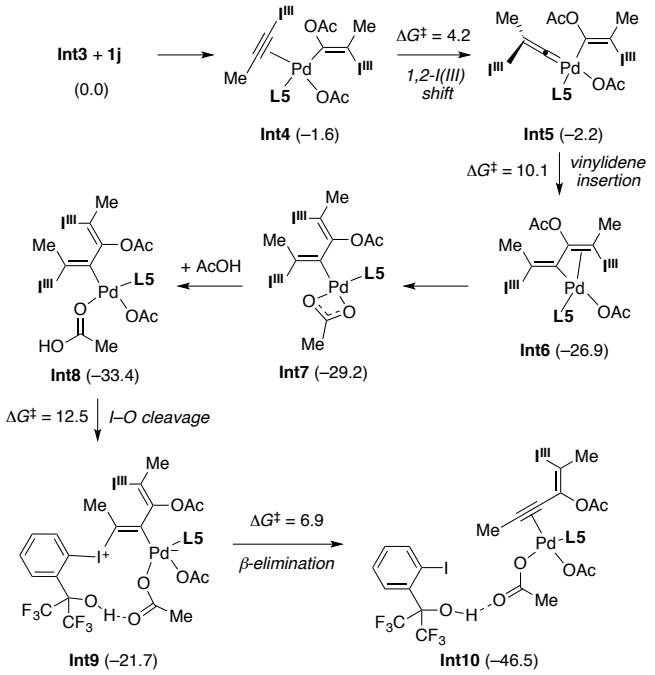


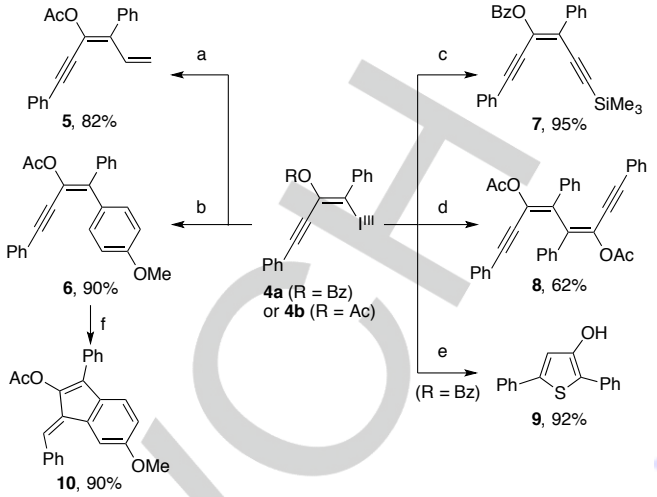
Figure 1. (a) Energy profile of the 1,2-I(III) shift and the migratory insertion. (b) DFT-optimized molecular structures. Color code: grey = C; white = H; purple = I; blue = N; red = O; turquoise = Pd. Substituents of the benziodoxole moiety are omitted for clarity (see the SI for computational details).

Further DFT studies allowed us to identify a viable pathway for the conversion of **Int3** into the carboxyalkynylation product (Scheme 3). The early stage of the pathway is mechanistically analogous to the pathway for the conversion of Pd(**L5**)$(OAc)_2$ and **1j** to **Int3**. Thus, a π-complex between **Int3** and another molecule of **1j** (**Int4**) undergoes 1,2-I(III) shift to give a new vinylidene/alkenyl–Pd species **Int5**, followed by insertion of the vinylidene moiety into the Pd–alkenyl bond. The resulting intermediate **Int6**, upon isomerization and incorporation of one molecule of AcOH, gives a tetracoordinate 1,4-diiodo(III)dien-2-yl–Pd species **Int8**, which then undergoes stepwise β-elimination. Thus, the AcOH molecule initially assists cleavage of the I–O bond of the benziodoxole moiety, and subsequent cleavages of the C–I and C–Pd bonds affords the product complex **Int10**, which comprises the 1,1-carboxyalkynylation product, Pd(**L5**)$(OAc)_2$, and 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol. In addition to this reaction pathway, we conceived two alternative pathways of alkynyl group transfer to **Int3**, one involving oxidative addition of **1j** to **Int3** and the other involving migratory insertion of **1j** into the alkenyl–Pd bond of **Int3** (see the Supporting Information for detail). However, these alternatives are considered less likely because of the high instability of the putative Pd(IV) intermediate (for the former pathway) or in light of the ^{13}C-labeling experiment (Scheme 2, for the latter pathway).



Scheme 3. Calculated pathway for the conversion of β-iodo(III)alkenylpalladium species **Int3** into the carboxyalkynylation product. (Relative) free energies shown in the parentheses and above the arrows are given in kcal mol^{-1}.

The functionalized enyne products obtained by the present reaction could be used as versatile building blocks for further transformations, as demonstrated by selected follow-up reactions of **4a** and **4b** (Scheme 4). Even in the sterically demanding tetrasubstituted environment, the benziodoxole moiety served as an excellent leaving group in Pd-catalyzed Stille, Suzuki–Miyaura, and Sonogashira couplings,[15] which afforded stereochemically well-defined multisubstituted dienyne **5**, enyne **6**, and endiyne **7**, respectively, in high yields. Pd catalysis also allowed reductive homocoupling of **4b** using Zn as a reductant, affording dienediyne **8** in 62% yield. In addition, exposure of **4a** to sodium sulfide caused a thiolative cyclization, with concomitant debenzoylation, to produce 3-hydroxythiophene derivative **9** in 92% yield. The Suzuki–Miyaura product **6** was amenable to gold-catalyzed cycloisomerization,[16] cleanly furnishing a benzofulvene derivative **10**.



Scheme 4. Selected product transformations. Reaction conditions: (a) $PdCl_2(PhCN)_2$, $(CH_2{=}CH)SnBu_3$, DMF, rt, 12 h; (b) $Pd(OAc)_2$, P(*t*-Bu)$_3$, 4-$MeOC_6H_4B(OH)_2$, LiOH, DME/H_2O, rt, 12 h; (c) $PdCl_2(PPh_3)_2$, CuI, Et_3N, trimethylsilylacetylene, DMF, rt, 12 h; (d) $Pd(acac)_2$, Zn, THF, 50 °C, 24 h; (e) $Na_2S{\bullet}9H_2O$, DMF/H_2O, rt, 2 h; (f) Ph_3PAuCl, $AgSbF_6$, CH_2Cl_2, rt, 20 min.

In summary, we have developed a palladium-catalyzed 2:1 coupling reaction between alkynylbenziodoxole and carboxylic acid, which features a mechanistically unique 1,2-I(III) shift/1,1-carboxyalkynylation sequence and affords a novel (alk-1-en-3-ynyl)benziodoxole. Regardless of the high propensity of the alkynylbenziodoxole toward decomposition in the presence of Pd(II), the reaction is achieved efficiently using octahydrophenazine as the supporting ligand. The origin of the ligand effect on the reaction efficacy and the chemoselectivity (vs. 1,1-hydrocarboxylation) remains unclear and warrants further experimental and theoretical studies. The alkynyl group transfer initiated by 1,2-I(III) shift (Scheme 3) may deserve to be considered as a mechanistic possibility in other transition metal-catalyzed alkynylations employing alkynylbenziodoxol(on)es.[6a,11] Further application of the present iodo(III)enyne products to the synthesis of novel π-conjugated compounds is also under investigation.

Acknowledgements

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Keywords: hypervalent iodine • palladium • carboxylic acid • alkynylation • cross-coupling

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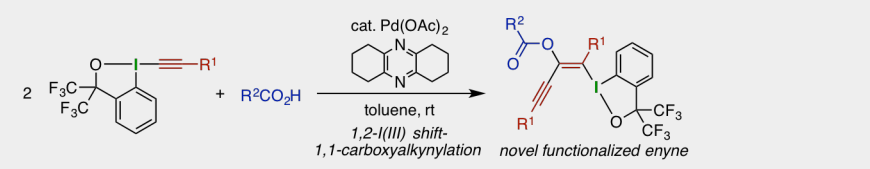

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Pd-Catalyzed, Ligand-Enabled Stereoselective 1,2-Iodine(III) Shift/1,1-Carboxyalkynylation of Alkynylbenziodoxoles

A Pd(II)–octahydrophenazine catalyst promotes 2:1 coupling of alkynylbenziodoxole with carboxylic acid. The reaction involves Pd(II)-assisted 1,2-iodine(III) shift of the alkynylbenziodoxole followed by stereoselective introduction of carboxy and alkynyl groups into the 1-position of the transient Pd–vinylidene species. The product of this 1,1-carboxyalkynylation reaction serves as a novel functionalized enyne-type building block for further synthetic transformations.