Organic Syntheses

Discussion Addendum for:

Synthesis of Substituted Indazoles *via* [3 + 2] Cycloaddition of Benzyne and Diazo Compounds

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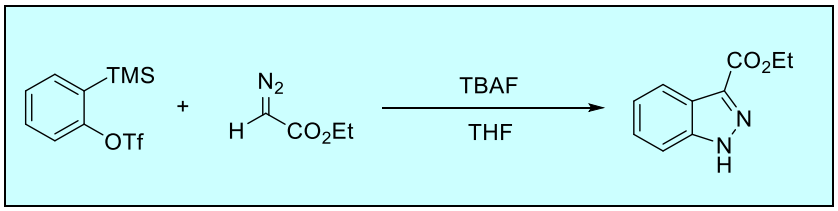

The use of benzyne annulation chemistry for the construction of *N*-containing heterocycles has seen significant growth in the literature in the last 15 years. One of the practical routes to these heterocycles begins with a [3 + 2] cycloaddition of benzyne (generated *in situ* from *o*-silylaryl triflates and fluoride ion) and diazo compounds. As reported by the Larock group,[2] the initial adduct, 3*H*-indazole, may further rearrange to form 1*H*-indazole (it depends on the nature of the diazo compound and the substituents on the benzyne). Our 2010 *Organic Syntheses* report[3] presents a large-scale synthesis (4.98 g) of a 1*H*-indazole derivative from ethyl diazoacetate. After this article, additional approaches to a family of indazoles (1*H*, 2*H*, and 3*H*) have been published, starting from *o*-silylaryl triflates and diazo compounds. This discussion addendum is intended to cover these reports.

Topics covered will be:

- Reaction of benzynes with monosubstituted diazo derivatives;
- Reaction of benzynes with disubstituted diazo derivatives;
- Reaction of benzynes with α-diazo phosphonates.

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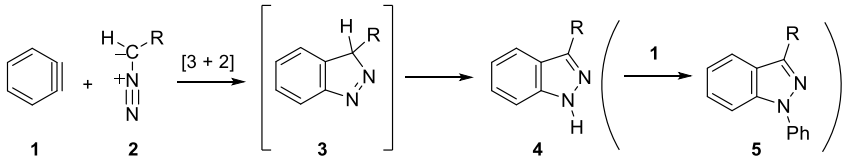
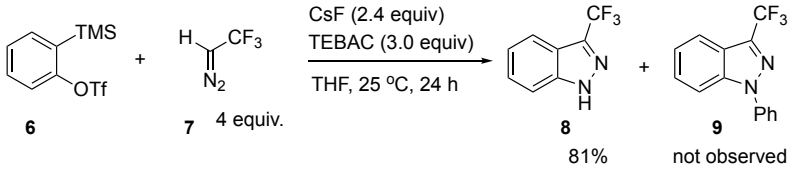
Reaction of Benzynes with Monosubstituted Diazo Derivatives

As the early reports by Yamamoto[4,5] and Larock[2] disclose, the reaction of benzynes (such as **1**) with monosubstituted diazo compounds **2** always leads to 1*H*-indazoles **4**, as a result of rearrangement of the initially formed 3*H*-indazole **3** to the 1*H*-indazole **4** during the course of the reaction (Scheme 1). The rearrangement is supposedly a 1,3-hydrogen shift, or a series of two 1,5-hydrogen shifts. The difference between Yamamoto's and Larock's reports is in that the former[4,5] utilizes KF in THF at room temperature with an 18-crown-6 additive, while the latter[2] utilizes TBAF in THF at –78 °C followed by warming up to room temperature. Furthermore, if an excess of benzyne is present, the free *N*-H indazole **4** is further converted to an *N*-arylated derivative (**5**, in the case of the unsubstituted benzyne); a closely related transformation has been reported as a standalone procedure in 2006.[6] In both Yamamoto's and Larock's reports, the *in situ* formation of **5** has been achieved using 2 or more equiv of the benzyne precursor in the presence of CsF in CH_3CN at room temperature. Both procedures taken together allow one to obtain 1*H*-indazoles (free and arylated) with R = ester, ketone, and Ph, in 56–97% yields, using an unsubstituted benzyne. Using both procedures, TMS-substituted diazomethane (**2**, R = TMS) afforded a desilylated product (**4**, R = H) in a lower yield (43–50%), with addition of CH_3OH to the reaction mixture being necessary.



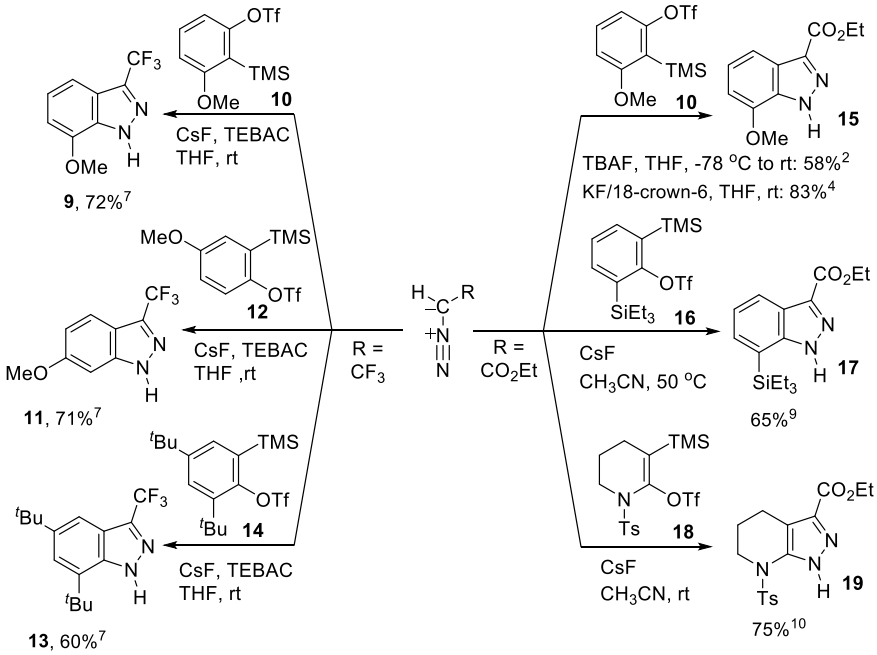
Scheme 1. Initial syntheses of 1*H*-indazoles by Larock and Yamamoto

The scope of the overall transformation was expanded in 2015, when Ma reported the reaction of CF_3CHN_2 (**7**) with *o*-silylaryl triflates (Scheme 2).[7] In this case, running the reaction in THF at room temperature in the presence of CsF and a common phase transfer catalyst, $[Et_3NBn]Cl$ (TEBAC), provided the highest yield, 81% using the unsubstituted benzyne precursor **6**. Perhaps due to the relatively large ratio of the diazo compound to the benzyne precursor (4/1), formation of the over-arylated indazole (**9**) has not been observed.



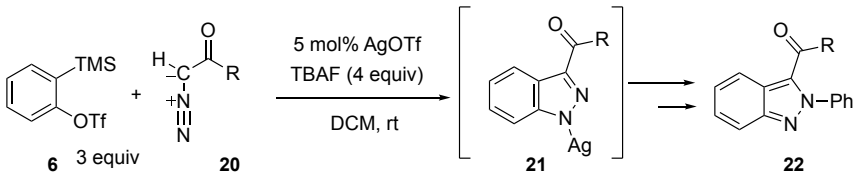
Scheme 2. Synthesis of 3-trifluoromethyl-1*H*-indazoles by Ma

Monosubstituted diazo derivatives successfully react with substituted benzyne precursors, as demonstrated in all three reports mentioned above (Larock,[2] Yamamoto,[4,5] and Ma[7]). In most cases the yields are somewhat (10–20%, on average) lower than with the parent benzyne and a mixture of regioisomers is usually observed with unsymmetrical benzynes. It is noteworthy that there are some exceptions to this generalization, as presented in Scheme 3. As such, 3-methoxybenzyne (derived from **10**) cleanly afforded products **9** and **15** as single regioisomers with both CF_3CHN_2 and ethyl diazoacetate, as did 4-methoxybenzyne (derived from *o*-silylaryl triflate **12**) in its reaction with CF_3CHN_2. In both cases, the observed regioselectivity is analogous to the reported coupling of these benzynes with other 1,3-dipoles and nucleophiles.[6,8] 4,6-Di-*tert*-butyl-substituted aryne precursor **14** resulted in a single isomer as well, likely due to its steric hindrance. Garg reported a single regioisomeric indazole **17** in 65% yield, starting from 3-(triethylsilyl)benzyne (derived from *o*-silylaryl triflate **16**), also presumably due to steric reasons.[9] Finally, Danheiser in his 2014 study of a strained ynamide (accessible from **18**), reports the clean formation of heterocycle **19** as a single regioisomer, upon coupling of the strained *N*-tosyl-3-azacyclohexyne with ethyl diazoacetate.[10]



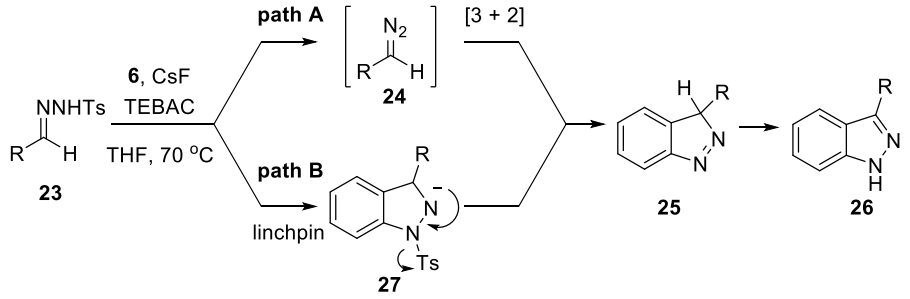
Scheme 3. Reaction of diazo compounds with substituted benzynes and an analogue

An interesting extension of the process shown in Scheme 1 was reported in 2012 by Liu and co-workers,[11] who performed the cycloaddition of monosubstituted diazo ketones **20** with benzyne in the presence of AgOTf (Scheme 4). The silver ion effectively blocked the *N*-1 atom of the initially formed 1*H*-indazole (presumably forming complex **21**), causing the extra benzyne intermediate (3 equiv were used in the process) to arylate *N*-2. As a result, 2-aryl-2*H*-indazoles **22** were formed (one entry's structure was confirmed by X-ray analysis). Optimal conditions (TBAF in CH_2Cl_2 at room temperature, in the presence of 5 mol% of AgOTf) allows one to obtain 2-phenyl-3-ketoindazoles with aryl (72–95%), heteroaryl (49–62%) and cinnamyl (44%) functionality. The use of a diazo ester (R = CO_2CH_2Ph) resulted in formation of 2-phenyl- and 1-phenyl- (inefficient Ag^+ blockage presumably) indazoles in 4/1 to 5/1 ratios, with an increased selectivity at higher loadings of AgOTf catalyst.



Scheme 4. Synthesis of 2*H*-indazoles by Liu

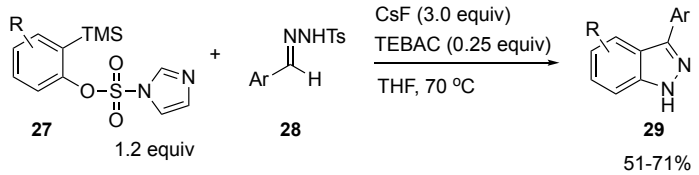
Shi and Larock envisioned that diazo coupling partners can be generated *in situ* from stable and readily available *N*-tosylhydrazones **23**.[12] Indeed, by reacting *o*-silylaryl triflates (such as **6**) with 10 different *N*-tosylhydrazones in the presence of CsF and [Et_3NBn]Cl (TEBAC) in THF at 70 °C, the desired 1*H*-indazoles **26** were produced in generally good yields, with only trace amounts of over-arylated products (Scheme 5). The reaction has been most successful with aryl-substituted *N*-Ts hydrazones (56–85% yields). Pyridine-3-carbaldehyde-derived hydrazone provided a 68% yield of the product, but thiophene-2-carbaldehyde-derived hydrazone gave only a 36% yield of the indazole, and pivalaldehyde *N*-tosylhydrazone resulted in only a 33% yield. It is noteworthy that *N*-Ts hydrazones derived from aliphatic aldehydes and alkenyl aldehydes did not prove effective in the transformation. While an alternative route (Scheme 5, path B) is not ruled out, a strong absorption at 2053 cm^{-1} in the IR and the overall outcome of the reaction with the unsymmetrical benzyne suggests that the major pathway in this process proceeds through formation of the intermediate diazo compound (path A).[13]



Scheme 5. Synthesis of 1*H*-indazoles from *N*-tosylhydrazones by Shi and Larock

In 2012, Novák and co-workers employed a new imidazolylsulfonate-based benzyne precursor **27** in a coupling with several *N*-tosylhydrazones (**28**) under Shi and Larock's conditions (Scheme 6). The authors were able to

successfully prepare a series of 1*H*-indazoles **29** (6 examples, 51–71% yields, EWG and EDG groups on the aryl ring are tolerated).[14]



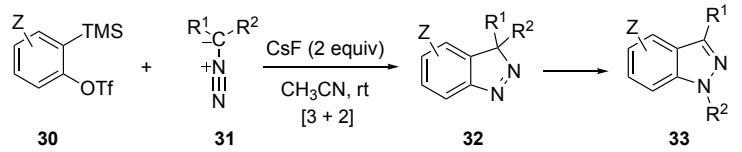
Scheme 6. Synthesis of 1*H*-indazoles using an imidazolylsulfonate benzyne precursor by Novák

Reaction of Benzynes with Disubstituted Diazo Derivatives

As our lab showed in 2008,[2] stabilized disubstituted diazomethane derivatives **31** provide 3,3-disubstituted 3*H*-indazoles, [3 + 2] cycloaddition products **32**, upon their coupling with *o*-silylaryl triflates **30** in the presence of CsF in CH_3CN at room temperature (Scheme 7). For example, when one of the substituents is a Ph or CH_2Ph group and another substituent is Ph or ester, 3,3-disubstituted 3*H*-indazoles **32** are produced in 44–87% yields. However, in many cases the carbonyl-containing functional group further undergoes an overall 1,3-migration, and *N*-substituted 1*H*-indazoles **33** are produced. The mechanism of the migration (**32** to **33**) is not clear, but is suggested to be a Fries-like ionization-recombination mechanism.[15,2] In the case with R^1 = Ph and R^2 = CO_2Et, the regular [3 + 2] product (**32**) was formed in a 72% yield, while the rearranged product (**33**) was formed in a 25% yield. Interestingly, in 2018, a change in conditions to TBAF/acetone at 0 °C allowed Peng and co-workers to isolate a similar 3*H*-indazole **32** (R^1 = Ph and R^2 = CO_2Me) in an 85% yield, with no mention of any rearranged product being formed.[16] In contrast, if this diazo derivative is generated *in situ* from the *N*-Ts hydrazone, exclusive migration of the ester group was observed, as reported by Shi, to form the corresponding 1*H*-indazole derivative **33** in a 63% yield.[13]

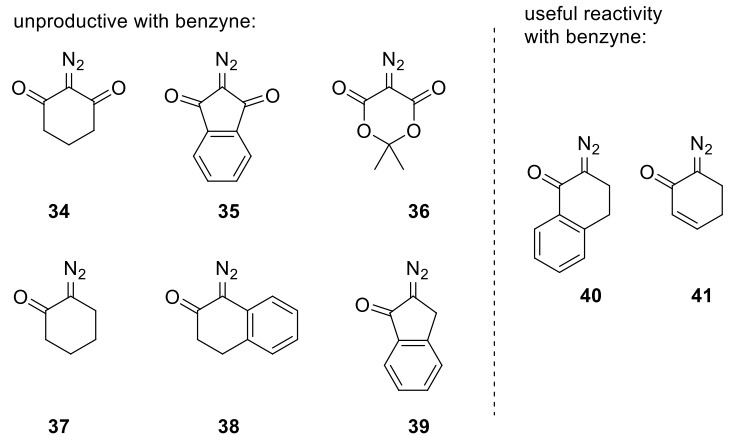
In the case of diazo substrates containing a ketone group, rearranged products **33** (*N*-keto 1*H*-indazoles) were the only products isolated using the Larock procedure.[2] A ketone functional group seems to selectively migrate in the presence of an ester, amide, and aryl group. The resulting products were cleanly produced in 83–92% yields. If both substituents are ketone groups (acetyl) or both are ester groups (CO_2Et), one of those groups migrates during the reaction, producing *N*-keto 1*H*-indazoles (**33**, R^1 = ketone, 97% yield) or

N-ester 1*H*-indazoles (**33**, R^1 = ester, 85% yield). The use of Shi's procedure[13] and ketone-containing *N*-Ts hydrazones as surrogates for diazo compounds resulted in complex mixtures under the reaction conditions.



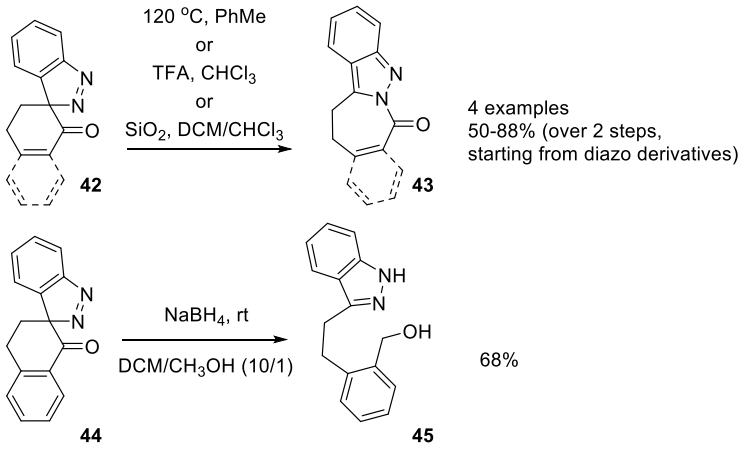
Scheme 7. Reaction of disubstituted diazomethanes with benzyne precursors

It is noteworthy that cyclic diazo compounds stabilized by two ketone or ester groups (**34**-**36**) have been recovered unreacted after the reaction under Larock's conditions[2] (Scheme 8). Similarly, in 2017 Zhai and co-workers reported **34** to be unreactive and **37**-**39** to produce complex mixtures upon reaction with the benzyne precursor in the presence of TBAT (tetrabutylammonium triphenyldifluorosilicate) in CH_3CN.[17] Interestingly though, the structurally related cyclic diazo ketones **40** and **41** provided [3 + 2] cycloaddition products with benzyne in 93 and 79% yields respectively.



Scheme 8. Cyclic diazo compounds explored in their coupling with benzyne

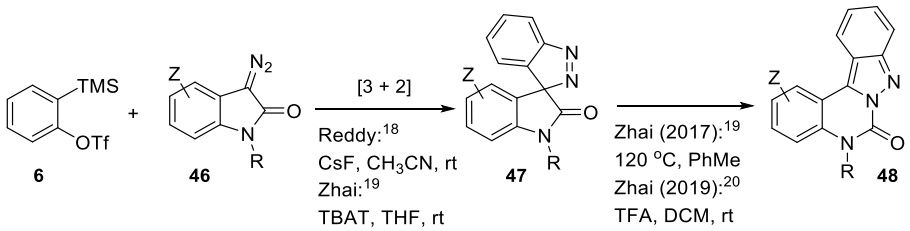
In their article, Zhai and co-workers reported the scope of this useful transformation and were able to successfully engage 8-substituted derivatives of **40** and **41** to produce the corresponding spiroindazoles in 66–95% yields.[17] Some of these spiro-3*H*-indazoles (**42**) could further be rearranged to fused 2*H*-indazoles **43** *via* heat- (120 °C in toluene) or acid- (TFA, weakly acidic silica and $CHCl_3$) mediated rearrangement (Scheme 9). Additionally, one spiro-3*H*-indazole (**44**) was reduced to a functionalized 1*H*-indazole **45** with $NaBH_4$ in DCM/CH_3OH (68% yield, structure confirmed by X-ray analysis).



Scheme 9. Reactions spiroindazoles by Zhai

Similarly, 3-diazoindolin-2-ones (**46**) undergo a [3 + 2] coupling with benzyne (Scheme 10). In 2017, Reddy and co-workers were able to produce spirooxindoles **47** in 75–92% yields using CsF in CH_3CN at room temperature.[18] The reaction tolerated methoxy, nitro, and halide substituents, and the *N* atom could be unprotected (*N*-H), as well as substituted (R = methyl, ethyl, propargyl, allyl, benzyl, and phenyl). Zhai and co-workers reported an alternative set of conditions, TBAT in THF at room temperature, which allowed them to produce spirooxindoles **47** in 80–98% yields with a similar transformation scope.[19] Under the reaction conditions, *N*-H, *N*-Ac, and *N*-Ts substrates did not result in the desired product. Interestingly, Zhai and co-workers also reported isomerization of the spirooxindoles **47** produced into fused 2*H*-indazole derivatives **48** (indalozo[2,3-*c*]quinazolin-

6(5*H*)-ones) under thermal conditions (heating at 120 °C in toluene). Eight derivatives **48** were successfully produced in 85–99% yields; one of the products was characterized by X-ray crystallography.



Scheme 10. Synthesis of fused 2*H*-indazole derivatives by Zhai

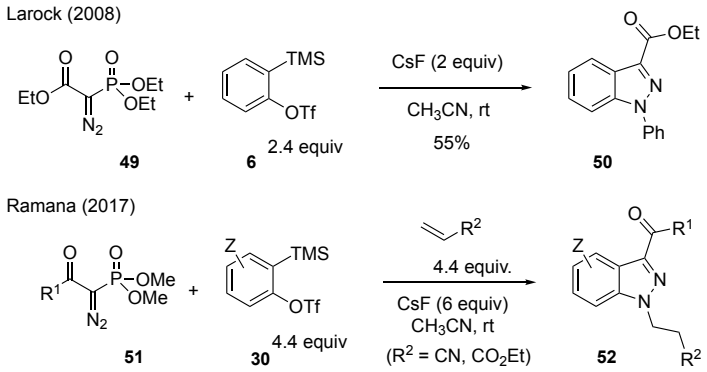
Recently, Zhai and co-workers extended the scope of their original transformation (Scheme 10)[20] to include *N*-PMB and *N*-MOM derivatives **46**, but the authors were also able to isomerize spirooxindoles **47** into indalozo[2,3-*c*]quinazolin-6(5*H*)-ones **48** upon milder reaction conditions (TFA in DCM at room temperature), rather than heating them at 120 °C. In fact, the two steps could be successfully combined into a one-pot procedure (93% yield overall, on a model substrate). They were also able to extend the reaction to eight examples of C=NTs and C=NMs analogues of 3-diazoindolin-2-ones (**46**) and produce the corresponding products in 49–70% yields. It is noteworthy that the resulting derivatives were quite stable under thermal or acidic conditions (*i.e.*, did not rearrange to analogs of **48**).

Reaction of Benzynes with α-Diazo Phosphonates

In 2008, Larock and co-workers disclosed that the reaction of triethyl diazophosphonoacetate (**49**) with excess benzyne precursor (2.4 equiv) conveniently affords an *N*-phenyl 1*H*-indazole **50** in a 55% yield (Scheme 11).[2] It was not clear at the time at which stage the phosphonate group is lost, prior to or after the [3 + 2] cycloaddition.

In 2017, Ramana and co-workers investigated the reaction of analogs of the Ohira-Bestmann reagent (OBR) (**51**) with a benzyne precursor and several Michael acceptors in the presence of CsF in CH_3CN (Scheme 11).[21] OBR, widely known for its utility in alkyne synthesis,[22] is known to undergo a base-

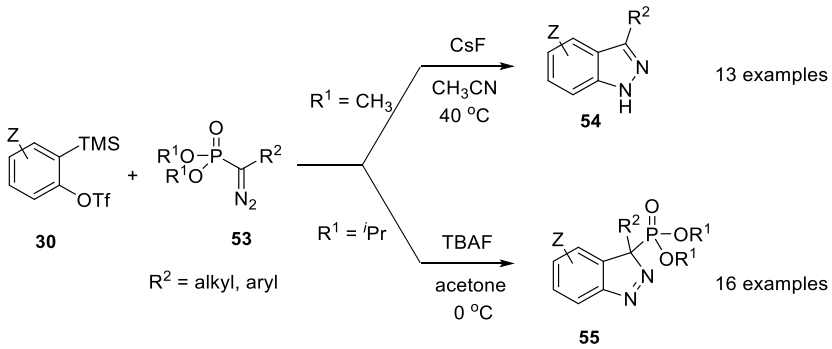
mediated loss of the acyl group in the first step of its reactions. Authors have argued that by exchanging the traditional alkoxide base for a fluoride (which, on one hand, is not as basic but, on the other, has high affinity for a phosphorous atom) it should be possible to cause OBR to lose the phosphonate, and not the acyl group. Indeed, this seems to be the case. The coupling of analogs of OBR (**51**) with *o*-silylaryl triflates (**30**) in the presence of CsF in CH_3CN has produced 1*H*-indazoles **52** in 68–85% yields, consistent with the earlier Larock findings.[2] In all cases, to avoid over-arylation (at the *N* atom), excess of a Michael acceptor (4.4 equiv of methyl acrylate or acrylonitrile) has been used, thus producing *N*-alkylated versions of 1*H*-indazoles **52**. Alkyl, aryl, and heteroaryl (indolyl) ketone analogs of OBR have reacted with similar efficiency. Using an ester rather than a ketone (**51**, R^1 = OEt) significantly decreased the yield (31%) of this transformation. Mechanistic investigations conducted by Ramana suggest that loss of the phosphonate group from the OBR occurs within two hours under the reaction conditions (CsF, CH_3CN, room temperature) and, while it does not prove that the group is lost exclusively before the [3 + 2] cycloaddition with the benzyne, it provides a plausible mechanistic explanation for the reaction's outcome.



Scheme 11. Reaction of α-diazo phosphonates with benzynes

In 2018, Peng and co-authors disclosed that the reaction of dimethyl α-diazo phosphonates (**53**, R^1 = CH_3) with the benzyne precursor under a variety of fluoride-containing conditions consistently provided 1*H*-indazoles **54** (Scheme 12).[23] In all cases, the phosphonate group was lost (consistent with Larock and Ramana) and, interestingly, no *N*-arylation products were

observed. The optimal set of conditions, CsF in CH_3CN at 40 °C, allowed the authors to obtain 1*H*-indazoles **54** with 3-aryl substitution (64–96% yields) and 3-alkyl substitution (82–92%). Note that these 3-alkyl-1*H*-indazoles are difficult to obtain; this procedure is one of the few examples among the papers reviewed in this addendum to accomplish that, along with the route to 3-CF_3 indazoles reported by Ma.[7]



Scheme 12. Synthesis of 1*H*-indazoles and 3*H*-indazole-3-phosphonates by Peng

Furthermore, Peng and co-workers envisioned that by modifying the phosphonate group, its loss (or migration followed by loss) could be suppressed. Indeed, by switching to diisopropyl α-diazo phosphonates (**53**, $R^1 = {}^i$Pr, instead of the dimethyl-containing original substrates, the authors were able to suppress the migration and form diisopropyl 3-alkyl and aryl-3*H*-indazole-3-phosphonates **55** in 91–99% (for alkyl) and 75–96% (for aryl) yields. The optimal set of conditions was found to be TBAF in acetone at 0 °C. The reaction works reasonably well with a substituted electron-rich dioxolane-containing benzyne (88%) but is less efficient with the electron-deficient difluorobenzyne (47%, common trend in benzyne chemistry). Peng's method seems to be the first example of the synthesis of 3*H*-indazole-3-phosphonates, substrates that combine two medicinally interesting scaffolds, an indazole and a phosphonate.

Concluding Remarks

The field of benzyne-mediated transformations has continued its growth in the last decade. More and more procedures have appeared in the literature

that allow the conversion of readily available starting materials into much more complex molecules, particularly, nitrogen-containing heterocycles. One can see from the discussion addendum how every reported finding increases the scope and efficiency of prior work and opens up new synthetic pathways to previously inaccessible structural frameworks. The ease of accessing these heterocyclic frameworks, many of which have established or potential bioactivity, will undoubtedly contribute to the future of medicinal chemistry.

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Richard C. Larock is Distinguished Professor and University Professor Emeritus at Iowa State University where he taught from 1972 to 2011. He received his B. S. at the University of California at Davis in 1967 and his Ph.D. in 1972, under the direction of Prof. Herbert C. Brown. He then worked as an NSF Post-doctoral Fellow at Harvard University in Prof. E. J. Corey's group. Prof. Larock is a pioneer in the use of palladium catalysts in organic synthesis, particularly in the synthesis of carbocycles and heterocycles, and contributed also to the synthesis and characterization of biopolymers and biocomposites.