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Hydrogen-Atom-Transfer-Initiated Radical/Polar Crossover Annulation Cascade for Expedient Access to Complex Tetralins

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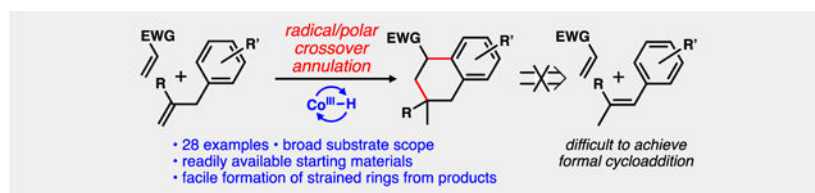
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Abstract

A radical/polar-crossover-based annulation between allyl-substituted arenes and electron-deficient alkenes is described. Cobalt-catalyzed hydrogen atom transfer (HAT) facilitates tandem radical C–C bond formation that generates functionalized tetralin products in the face of potentially problematic hydrofluorination, hydroalkoxylation, hydrogenation, alkene isomerization, and radical polymerization reactions. The reactions proceed under mild conditions that tolerate many functional groups, leading to broad substrate scope. This powerful ring-forming reaction very quickly assembles complex tetralins that are the formal products of the largely infeasible Diels–Alder cycloadditions of styrenes.

Graphical Abstract



A radical/polar crossover manifold permits annulations between allylarenes and Giese-type accepters, providing a route to functionalized tetralins. The reaction conditions are mild and therefore exhibit significant functional group tolerance. The annulation products are formally cycloadducts of styrenes and electron-deficient alkenes, and they can be used to form a variety of strained ring products.

Keywords

annulation; radical; hydrogen atom transfer; Giese addition; radical/polar crossover

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Synthetic methods that reliably and controllably construct multiple carbon–carbon bonds are among the most valuable in organic synthesis. Annulations, as stepwise alternatives to cycloadditions, exemplify this idea and are powerful tools for the rapid buildup of complexity, with the Robinson annulation^{www} as the quintessential exemplar.^[1] Creative sequences resulting in annulation were heavily explored by Piers and coworkers, who designed and developed a range of bifunctional nucleophile- and electrophile-bearing reagents that could engage substrates with complementary functionality.^[2] Presently, the application of both transition metal-mediated and radical-based chemistries alike enables new annulative processes.^[3]

Tetralins (benzocyclohexenes) are ubiquitous among structures of secondary metabolites and pharmaceutical compounds alike, so the importance of reactions that quickly provide access to these scaffolds cannot be overstated. Among many examples of critically important tetralin-containing compounds are: A-ring aromatic steroids, morphinans, aryltetralin lignins such as podophyllotoxin/Etoposide, 2-aminotetralins like sertraline/Zoloft, doxorubicin, and ergot alkaloids. In this report, we describe a novel radical/polar crossover-based annulation reaction that provides expedient access to a broad range of tetralins.

Inspired in part by recent reports from the groups of Shenvi^[4] and Shigehisa,^[5] we recently disclosed a method for stereoselective radical bicyclizations initiated by cobalt-catalyzed hydrogen atom transfer (HAT) (Figure 1, top).^[6] Subsequently, this method enabled concise syntheses of several abietane diterpenoid natural products.^[7,8] Owing to our initial design as a cationic process (for R = CH₃)—via HAT from cobalt to the alkene to generate a tertiary radical and radical/polar crossover by oxidation to the cation—canonical benzylgeraniol-like precursors were chosen as starting materials to engage in concerted bicyclizations that should take advantage of preorganization.^[9] However, mechanistic experiments provided strong empirical support for an alternative stepwise mechanism via radical intermediates.^[6] Therefore, we posited that other cyclization cascade types should be feasible using this chemistry since the stepwise pathway would not limit us to linear tethering of reactive groups, contrary to a concerted cationic process. In this report, we demonstrate that a reorganization of reactive functional groups can facilitate powerful annulation events initiated by similar HAT chemistry (Figure 1, bottom).^[10]

To test this hypothesis, a radical/polar crossover annulation reaction was designed wherein allyl-substituted arenes serve as readily accessible 4-carbon partners for reaction with commercially available electron-deficient alkenes. Conceptually, this accomplishes the formal Diels–Alder cycloaddition with rearomatization of styrenes (4 π component) with electron-deficient alkenes (2 π component); the corresponding pericyclic variant is a challenging reaction that is largely limited to systems involving tethered reactive groups, aryne intermediates, or radical cation intermediates generated by photoredox catalysis.^[11–15] Therefore, a mild, selective method to execute this type of transformation has broad potential utility for the formation of complex polycyclic architectures from simple starting materials. Furthermore, such a method would naturally benefit from the unique chemoselectivity characteristic of transformations operating within the radical manifold. While the tethered systems underwent chemoselective radical bicyclizations, we were aware that the intermolecular nature of the Giese-type reaction required for annulation could lead

to effective competition by hydrofluorination,^[16] hydroalkoxylation,^[17] hydrogenation,^[18] alkene isomerization,^[4] and radical polymerization events.^[19] Indeed, each of these reaction types are known under conditions closely related to those we have used in our previous bicyclization studies.

We first attempted annulation between acrylonitrile and methallyl-substituted arene **1** (Figure 2), whose pattern of π -electron-donating methoxy substituents performed favorably in our earlier bicyclization studies.^[6,7] Our starting point for optimization involved conditions that approximated those that worked best for the fully intramolecular bicyclization chemistry: a 1:1 stoichiometry of the two partners, 10 mol% of the Co(II)-salen precatalyst **C1**, with 3 equivalents each of silane reductant TMDSO (1,1,3,3-tetramethyldisiloxane) and *N*-fluorocollidinium tetrafluoroborate oxidant **Ox**, all in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) at 20 °C. The outcome proved promising. However, because the first C–C bond-formation is intermolecular, the lower effective concentration of radical acceptor led to many of the anticipated, problematic side reactions of **1** including hydrogenation, hydrofluorination, hydroalkoxylation, and alkene isomerization. Raising the concentration of acrylonitrile to ~5 equivalents proved optimal; with further increases, competing HAT to acrylonitrile appears to reduce efficiency.^[20] A modest increase in temperature was all that was needed to yield a highly effective annulation protocol.

Emboldened by our success with acrylonitrile, we sought to expand our optimization efforts to cyclohexenone as a representative cyclic radical acceptor that would afford polycyclic annulation products such as **3**. Direct application of the optimized conditions for acrylonitrile provided the tricyclic ketone product in only 27% yield, and **1** was isomerized to the corresponding styrene^[21] in significant quantities. We were cognizant that Giese acceptor reactivity is much lower with cyclic enones than with acrylonitrile, and that as a result the intermediate tertiary radical was more likely to befall other fates including back-HAT to form the styrene. This was supported by increased efficiency when catalyst loading was reduced, likely because the concentration of Co(II) species—that could remove the benzylic H atom—should be lower. Changing precatalyst had a more significant impact. The application of inexpensive salcomine (**C2**) completely mitigated styrene formation; however, reduction and hydrofluorination products reemerged. Decreasing both the quantity of oxidant **Ox** and the temperature led us to conditions that provided tricyclic ketone **3** in good yield and with a reasonable selectivity for the *cis* ring junction.^[22]

Although the data above show that there is a potential need to optimize the annulation reaction according to the identity of the radical acceptor, we limited ourselves to a small set of conditions in evaluating its scope and limitations. Most importantly, these data indicate the significance of several key parameters to overall reaction efficiency, and thus provide a useful starting point for others interested in applications of this methodology. A full treatise of the optimization and control studies in the development of this annulative process can be found in the Supporting Information.

Having established a pair of optimal reaction conditions, we examined the reaction scope with respect to each annulation component (Figure 3). On the left panel of the figure, acrylonitrile was used as the radical acceptor with varied allylarenes. While we optimized to

10 mol% catalyst **C1** for the rapid annulation with **1** to give **2**, in virtually all other cases where the reactions were slower, a lower catalyst loading (2 mol%) led to cleaner reactions owing to the elimination of undesired side products. Under these conditions, a chloroallyl substrate gave **4** in very high yield as a mixture of diastereomers. Simple allylarenes also worked (see **5**), but were more sluggish presumably owing to slower HAT from cobalt hydride, and thus only provided a modest yield of product. Benzylic oxygenation was tolerated in both unprotected and protected forms (**6** and **7**), and a terminal allylic alcohol substrate performed well to afford **8**. Likely owing to the early transition states of radical reactions, diastereoselectivities in relevant cases were not high. Next, the reaction was evaluated with a range of electron-rich and electron-neutral arenes (see **9** through **17**). Moderate to good yields are seen throughout the series that shows tolerance for methoxy groups at all positions (**9**, **11**, and **13**), free (**10**) and silylated phenols (**12**), the ubiquitous (in natural products) methylenedioxy group (**14**), and an aryl bromide (**15**). Interestingly, in the cases of differently substituted 3-phenols (**10–12**), the free phenol led to the most regioselective reaction, more so even than the bulky triisopropylsilyl-protected substrate. Finally, and not surprisingly, the reaction tolerated a naphthyl ring terminator and an indole; however, the latter was not an efficient participant unless N-tosylated (see **17** and **18**).

In the right-hand panel of Figure 3, we show the results of various radical acceptors paired, for the most part, with 1,3-dimethoxy-5-methallylbenzene (**1**). In cases with cyclic radical acceptors, without any optimization for each, moderate to good yields were seen with cyclohexenone, cyclopentenone, a cyclic enone made by Achmatowicz reaction, and maleimide (**3**, **19–21**, respectively). We also found that the chloroallyl arene we had used previously engages maleimide efficiently (**22**). Methacrylonitrile works well with both the methallyl substrate **1** to give **23**, and with the analogous chloroallyl reactant to afford **24** as a mixture of diastereomers. β -Substitution is tolerated as demonstrated by the reaction with crotononitrile (**25**). Some less efficient reactions included those with an alkylidene malonate to give **26** and with naphthoquinone to give tetracyclic compound **27**; these radical acceptors appear to suffer deleterious competitive reduction to ethyl diethylmalonate and naphthoquinol, respectively. Acrylamides are relatively ineffective radical acceptors (see **28**); in the case of the chloroallyl substrate, the product converted during isolation and purification to bridged lactone **30**. Polymerization of acrylamides under similar conditions is well established and appeared to compete with annulation.

A discussion of limitations of the annulation method can be broken down into the three reactive functional group components. First, the alkene initiator was limited to 1,1-dialkyl substitution (methallyl and allylically oxygenated variants), a terminal alkene (allylarene), or an alkenyl chloride (chloroallylarene); bromoalkenes, enoxysilanes, and alkenyl ethers were not viable substrates, with the latter two rapidly hydrolyzing to the ketones.^[23] Styrene substrates did not undergo an analogous reaction to form indane products. Second, while many typical Giese acceptors worked, several such reactants such as maleates, nitroalkenes, and azodicarboxylates did not lead to the desired annulated products.^[24] Finally, the presumed oxidative termination is best served by substrates wherein the arene terminator is electron-rich or electron-neutral.^[6] Electron-deficient arenes were not tolerated.

To the best of our knowledge, the products of our annulation process were all previously unknown. Furthermore, the products of the radical/polar crossover annulation can engage in potentially useful transformations. Some examples are shown in Figure 4, several of which take mixtures through stereoconvergent reactions to afford single products. The tertiary chloride of **4** can be reduced to give **5** as a diastereomeric mixture (and likely could undergo Giese reaction itself), but it can equally be transformed via transannular cyclization to cyclopropane **31**; both diastereomers of **4** converted via the same presumed nitrile-stabilized carbanion. Oxidative dehomologation of the nitrile^[25] proved to be facile, as exemplified by the reaction of **2** with base under an atmosphere of oxygen to give ketone **32**. The ease of this type of oxidation was discovered in an attempt to convert tosylates **33** to bridged cyclobutane **35**. We instead observed dehomologated fused cyclopropane **34**, which was formed stereoconvergently in preference to the cyclobutane **35**; with deliberate inclusion of O₂, this reaction formed **34** in preparatively useful yields. In an interesting twist, subsection of the diastereomeric mixture of bromides made from **33** to the same reaction conditions led to exclusive formation of cyclobutane **35**. The reactions that forge the congested fused cyclopropane **31** (vicinal quaternary stereogenic centers) and bridged cyclobutane **35** are further evidence of the utility of nitrile-stabilized anions in the formation of sterically encumbered C–C bonds.^[26]

Drawing similarities between this system and the bicyclizations that were examined previously by our group,^[6] we suggest a plausible mechanistic framework for the annulation (Figure 5). Initial HAT from Co(III)–H species generates the tertiary alkyl radical **I** that effects Giese addition, generating electron-deficient radical **II**. The subsequent dearomative cyclization—thought to be reversible on the basis of interesting stereochemical outcomes in the annulation of cyclohexanone^[23]—completes the annulation process with generation of cyclohexadienyl radical **III**. Our prior mechanistic studies suggest termination is facilitated by single electron oxidation of this radical followed by deprotonation of **IV**. Another possible fate of **III** is back-HAT to a cobalt complex as proposed by Shenvi;^[4] both pathways may be operative, and both ultimately converge to product **V**.

In summary, we have developed a Co-catalyzed, HAT-initiated annulation method that permits the union of allyl-substituted arenes and simple electron-deficient alkenes to form useful tetralin products. Conceptually, these tetralin products are congruent to the formal [4+2] cycloaddition products of styrenes and electron-deficient alkenes, a reaction type that is challenging to accomplish by other means. The method is operationally simple, proceeds under relatively mild conditions, and tolerates several important and sensitive functionalities. Mechanistically, the reaction likely proceeds via radical/polar crossover as informed by our prior studies, and applications are under investigation in our laboratory.^[27]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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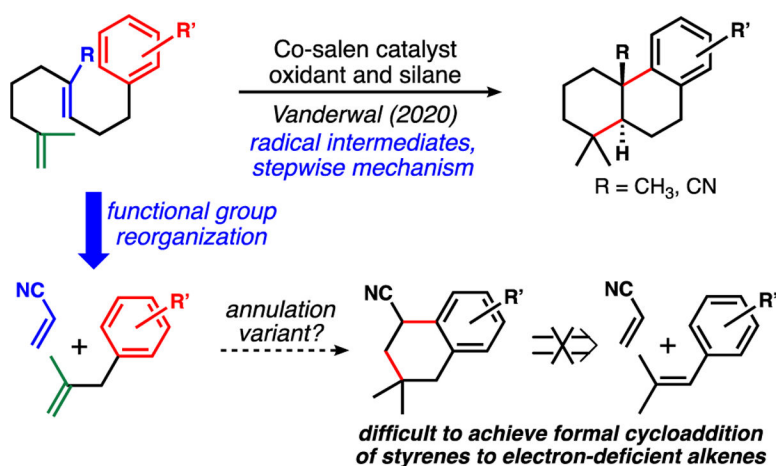
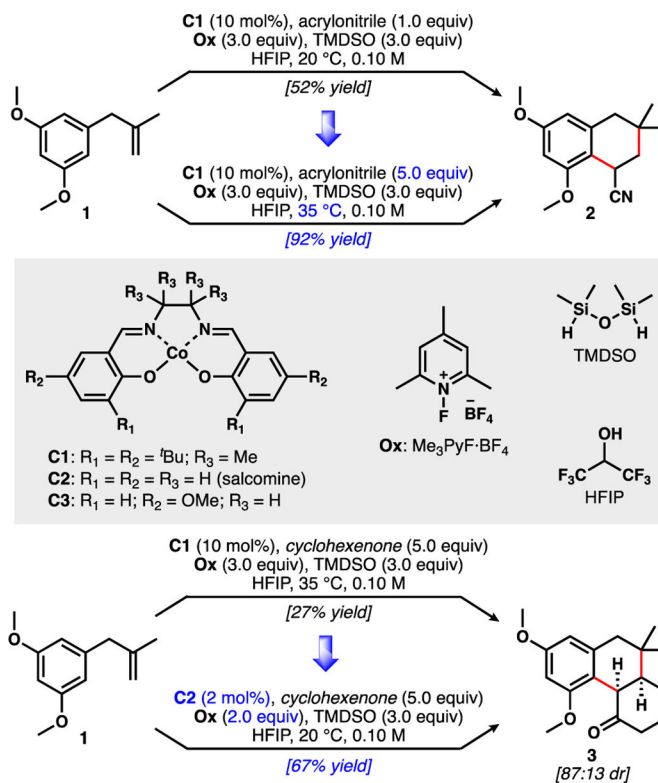
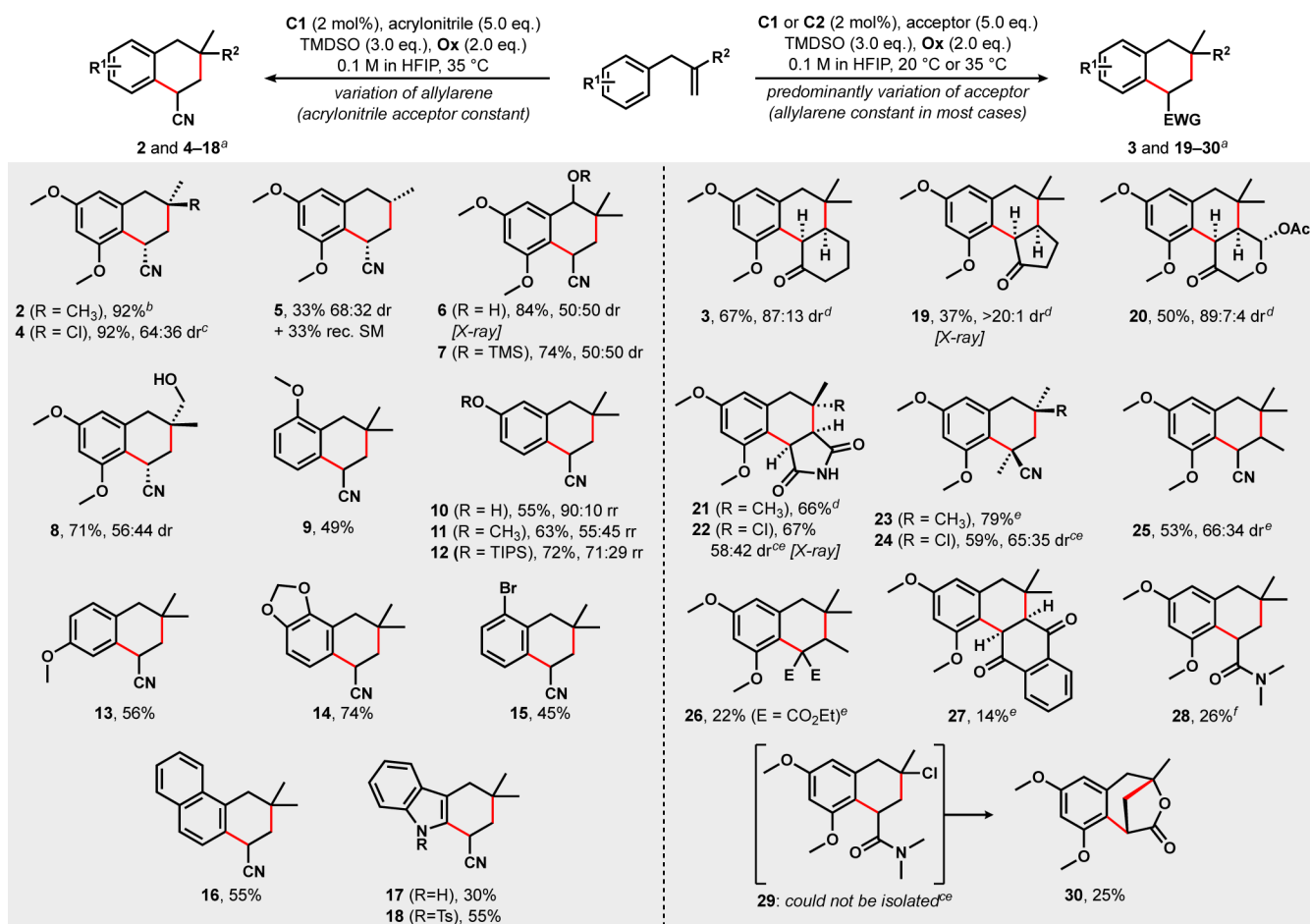


Figure 1. Conceptual reorganization of functional groups within canonical benzylgeraniol-like substrates provides a blueprint for a novel annulation cascade.

**Figure 2.**

Distinct reaction conditions for acrylonitrile and representative less reactive radical acceptor cyclohexenone



^awhen more than one regio- or stereoisomer is formed, the major product is shown; ^b10 mol% cat., 3 equiv oxidant; ^c0.3 M concentration of limiting reagent in HFIP; ^dC2, 20 °C; ^eC1, 35 °C; ^f0.02 M concentration of limiting reagent in HFIP, 2 equiv acceptor, 3 equiv oxidant.

Figure 3.

Scope of the annulation reaction between allylic arenes and Giese-type acceptors (dr: diastereomeric ratio; rr: regioisomeric ratio)

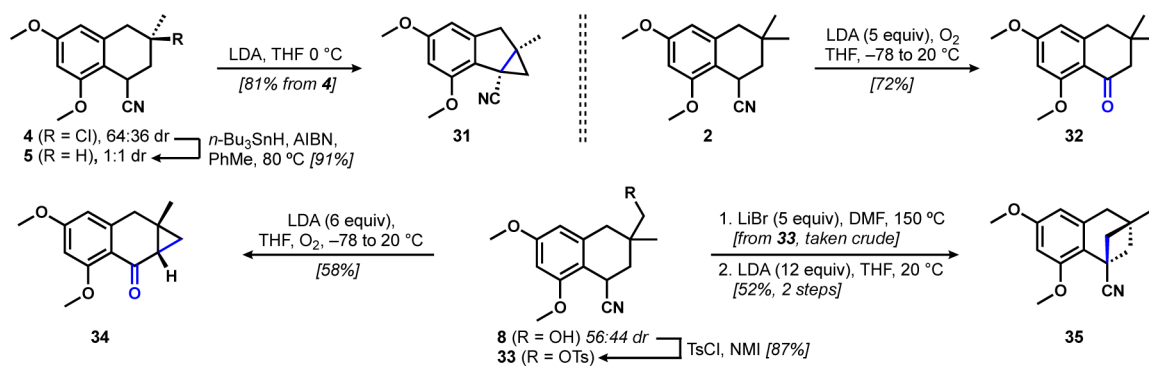


Figure 4.
Potentially valuable transformations of annulation products, including stereoconvergent cyclizations

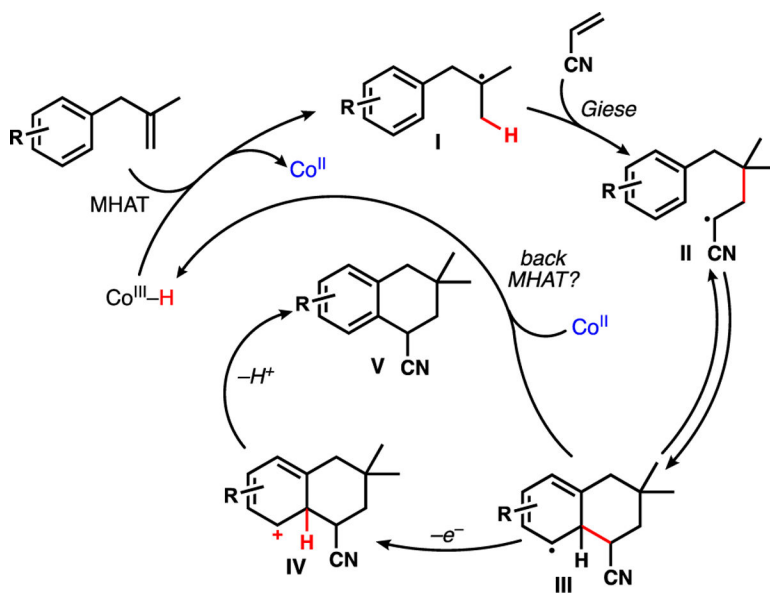


Figure 5.
Plausible reaction mechanism