Temperature-Dependent Diastereodivergent [4+3] Annulation: Synthesis of Ferrocene Fused Azepines *via* Rh(III)-Catalysis

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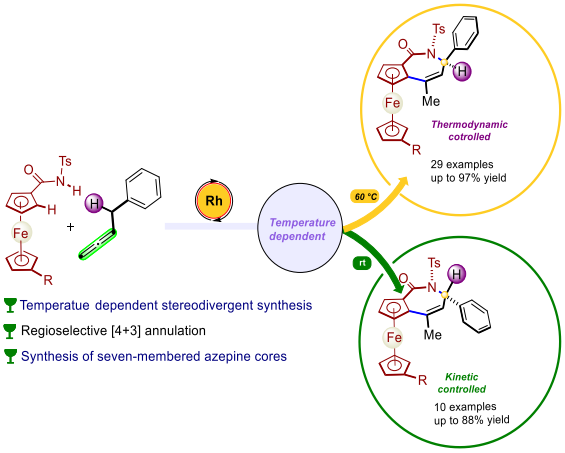
Supporting Information Placeholder

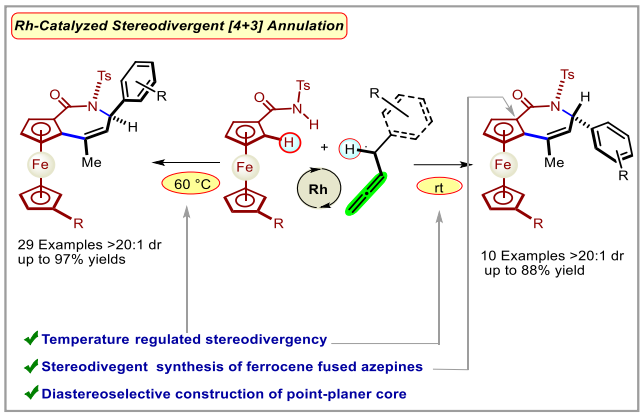


ABSTRACT: Herein, we disclose the first temperature-dependent diastereodivergent [4+3] annulation of ferrocene-*p*-tosylamides *via* C-H activation with allenes by Rh-catalyst. At room temperature, Rh-catalyzed [4+3] annulation selectively offered one diastereomer (>20:1 *dr*), whereas at 60 °C, another diastereomer was obtained exclusively with >20:1 *dr*. The control experiments, isotopic labeling study, and DFT calculations suggested that the reaction proceeds *via* a σ-bonded rhodacycle avoiding steric repulsion between the phenyl ring of allene and Cp* of Rh-catalyst. Consequently, reductive elimination offered a kinetically controlled diastereomer at room temperature. Under heating (60 °C) conditions, kinetically controlled diastereomer undergoes C-N bond ring opening to afford completely thermodynamically controlled diastereomer.

Ferrocene, an organometallic sandwich complex, shows very good stability and redox properties.[1-3] In recent decades, significant advances have been made in the field of transition metal TM-catalyzed asymmetric C-H activation to synthesize functionalized planar chiral ferrocenes.[4] Consequently, a variety of directing groups and coupling partners have been explored using Rh,[5] Co,[6] Pd,[7] Ir,[8] Pt,[9] and Sc[10]-based catalysis for various transformations namely arylation, alkylation intra, and intermolecular annulations for the synthesis of five and six-membered heterocyclic ferrocenes.[11] The installed planarity combined with point chirality leading to diastereomers in ferrocene offers additional support for achieving highly asymmetric transformations.[2b] However, the construction of dual planar and point chirality in a controlled manner is yet to be explored. Apparently, diastereodivergent catalysis is a rational way and emerged recently to synthesize all possible diastereomers.[12] However in the context of ferrocene, there is no report available on diastereodivergent leading to different stereoisomers.

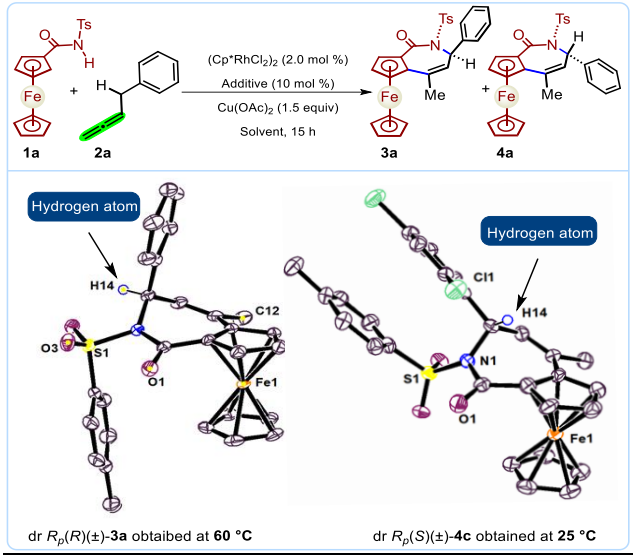
Previously our group has studied the C-H activation in ferrocene for the construction of carbon-carbon and carbon-heteroatom (heteroatom = S/Se/Te) bonds.[13] Further, a variety of directing groups have been studied along with various coupling partners, namely alkanes, arenes, aryl halides, alkenes, and alkynes with ferrocenes by others and us.[14] Thus we thought of choosing allene as a coupling partner which allows to a distinct regioselective mode of activation as well as multiple chiral center construction within one step.[15,16] Herein, we report for the first time a Rh-catalyzed temperature-dependent diastereodivergent synthesis of seven-membered ferrocene fused azepines by allene-driven [4+3] annulation (Scheme 1). This protocol enables the synthesis of kinetically and thermodynamically controlled diastereomers at room and high temperatures, respectively. Furthermore, the *N*-tosyl group has been removed after C-H functionalization.

Scheme 1. Synthesis of Ferrocene Fused Heterocycle



N-Tosylcarboxamide directing group (DG) was selected over earlier used bidentate *N*-8-aminoquinolinyl[13] and N-aryl/alkyl carboxamides DGs[13] to obtain the desirable selectivity and reactivity, respectively. A well-known bidentate *N*-8-aminoquinolinyl directing ligand facilitates C-H activation effectively and exhibits very good reactivity.[17] However, it offers poor selectivity, presumably due to the ligand rigidity. Consequently, *N*-tosylferrocene carboxamide substrate **1a** was prepared from ferrocenyl chloride and *p*-tosylsulfonamide in ethyl acetate solvent (See SI, page S6). We started our investigation for Rh-catalyzed annulation with *N*-tosylferrocene carboxamide **1a** and benzylallene **2a** as a model substrate in the presence of a mild oxidant AgOAc (Table 1 and SI, Tables S1-S4). The reaction was carried out in non-polar solvent toluene at 80 °C which resulted in a [4+3] fused azepine **3a** in 5% yield with excellent diastereoselectivity (*dr*) >20:1 (entry 1, Table 1). Further, we have tested the additive, AgOAc to enhance the yield of annulated azepine **3a**, however, only a small increment in the yield was observed (entry 2, Table 1). The formation of the cationic active rhodium catalyst may be required for the annulation. Consequently, a strong halide scavenger $AgBF_4$ was introduced to the reaction, leading to a further yield enhancement of **3a** to 22% (entry 3, Table 1). The unsatisfactory performance of toluene as a solvent in the reaction led us to conduct a systematic solvent screening. The coordinating polar aprotic nitrile solvents were found to be more effective than the others, affording **3a** in 46% yield, possibly due to their ability to stabilize the reactive intermediates involved in the [4+3] annulation. Further, $AgPF_6$ and $AgSbF_6$ halide scavengers were also evaluated in the reaction, which led to lower 35 and 40% yields of **3a**, respectively (entry 4). Previous literature[18] on allene transformations suggested that the reactivity of allenes could be a concern, as it readily undergoes degradation and polymerization at higher temperatures. Therefore, to mitigate these side reactions, lowering the temperature from 80 to 60 °C led to a moderate enhancement in the yield (65%) of **3a** (entry 5, Table 1). To our delight, an addition of NaOPiv salt (1.0 equiv) resulted in a very good yield (92%) with excellent *dr* (>20:1) of **3a** (entry 6, Table 1). Here, NaOPiv seems to act as an internal base in this reaction, which increases the rate of the concerted metalation deprotonation (CMD) step.[19] Additionally, it shifts the equilibrium towards the metallacycle formation (*vide infra*). Surprisingly, a decrease in the diastereomeric ratio (4.5:1) was realized when the reaction was conducted at 40 °C during the temperature optimization.

Table 1. Optimization of the Reaction Conditions for Rhodium-Catalyzed [4+3] Annulation[a]



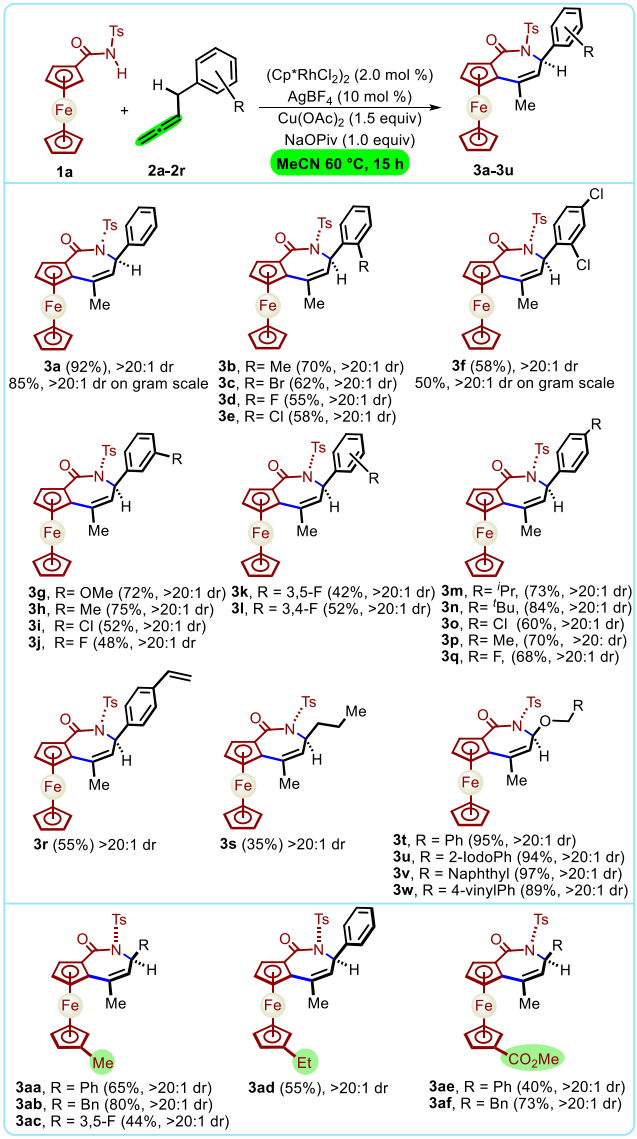
Entry	Additive	Solvent	Temp.	3a [b]	4a [b]
1	-	toluene	80	5	-
2	AgOAc	toluene	80	15	-
3	$AgBF_4$	toluene	80	22	-
4	$AgSbF_6$	MeCN	80	40	-
5	$AgBF_4$	MeCN	60	65	-
6[c]	**$AgBF_4$**	**MeCN**	**60**	**92**	**-**
7[c]	$AgBF_4$	MeCN	40	72	16
8[c]	**$AgBF_4$**	**MeCN**	**RT**	**-**	**88**

[a] Reaction conditions: **1a** (0.13 mmol), **2a** (0.26 mmol), $(Cp^*RhCl_2)_2$ (2.0 mol %), additive (10 mol %), $Cu(OAc)_2$ (1.5 equiv), 2.0 mL solvent at 60 °C under inert atmosphere. [b] Isolated % yields of **3a** and **4a**. [c] NaOPiv (1.0 equiv). ORTEP Views of **3a** and **4c** with 50% Ellipsoid Probability. The phenyl ring (from allene) in **3a** is situated above side, and hydrogen is downside. In the diastereomer **4c** which is obtained at 25 °C, the phenyl ring of allene is downside, and hydrogen is the upside.

Next, the reaction at room temperature resulted in another diastereomer **4a** in 88% yield with an excellent *dr* (>20:1, entry 8, Table 1) to our delight. Both diastereomers **3a** and **4a** were studied by single crystal X-ray diffraction analysis.

After optimizing the conditions for both diastereomers **3a** and **4a**, we investigated the scope of the reaction with regard to different allenes **2a-2s** at 60 °C (Scheme 2). Initially, in benzylallenes **2b**, ortho-methyl substitution provided a good yield of **3b** (70%) with an excellent *dr* >20:1. While allenes with electron-withdrawing bromo, fluoro, and chloro-substitution in phenyl ring provided [4+3] annulated ferrocene fused azepines **(3c-3f)** in moderate 55-62% yields with an excellent diastereomeric ratio >20:1. Further, meta-substitution in a phenyl ring with electron-donating groups (EDGs) provided moderate to good yields of **3g** (72%) and **3h** (75%).

Scheme 2. Substrate Scope with regards to Allenes for the Synthesis of Thermodynamically Controlled Diastereomers



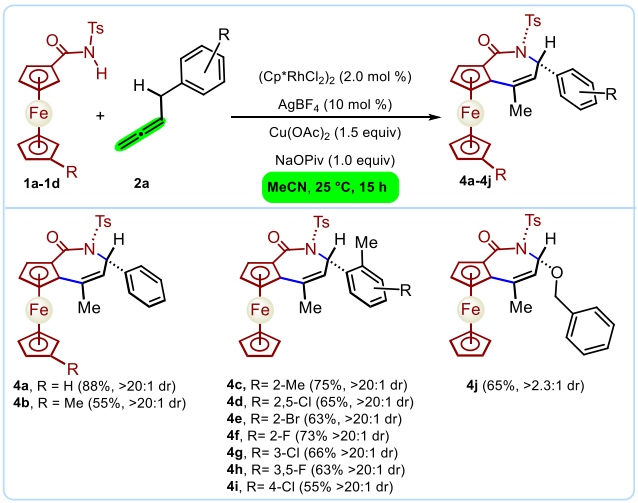
[a] Reaction conditions: amide **1a** (0.13 mmol), allenes **2a-2s** (0.26 mmol), $(Cp^*RhCl_2)_2$ (2.0 mol %), $AgBF_4$ (10 mol %), $Cu(OAc)_2$ (1.5 equiv), NaOPiv (1.0 equiv), CH_3CN (2.0 mL) at 60°C under inert atmosphere.

Conversely, electron-withdrawing groups at the *meta* position in phenyl allenes provided moderate yields (42-52%) of **3i-3l** with excellent *dr* (>20:1). Moreover, the para-substituted allenes **2r**, **2j**, **2s**, **2f** and **2i** with electron-donating methyl, isopropyl, tert-butyl and withdrawing fluoro and chloro substituents offered better yields (60-84%) of [4+3] annulated ferrocene fused azepines **3m-3q.**

We have also explored styrene-based allene **2m** substrate having alkene moiety under Rh-catalyzed [4+3] diastereoselective annulation reaction. To our delight, the reaction afforded the desired [4+3] ferrocene fused azepines **3r** chemoselectively, albeit a slight reduction in the yield (55%) was observed. The insight from the substitution in the phenyl ring of allene studies indicated that both electronic and steric factors seem important in Rh-catalyzed [4+3] annulation. However, steric factors appear to be more dominant than electronic factors. Next, aliphatic allene, a challenging substrate in Cp*M-catalyzed annulation, **2d** was subjected to [4+3] annulation reaction, which provided a poor yield (35%) of alkyl azepine **3s** (Scheme 2). Further, isopentyl allene reacted sluggishly in the reaction, and respective [4+3] annulated azepine could not be isolated, presumably due to the steric of isopropyl substituent. Desirably, heteroatom (benzyloxy, ortho-iodophenyl, naphthalene, and para-styrene) substituted allenes provided respective ferrocene fused azepines **3t-3w** in excellent yields (89-97%) and excellent >20:1 *dr*. A substantial increase in the yield using oxygen-heteroatom substituted benzyloxyallenes (Bn-O-CH_2-CH=C=CH_2) suggested that the high acidity of sp^3C–H bond in allenes could facilitate [4+3] annulation. Subsequently, the reactions of substituted *N*-tosylferrocene carboxamide having methyl and carboxymethyl on the second Cp ring were explored under the Rh-catalyzed reaction conditions (Scheme 2).

Alkyl-substituted *N*-tosylferrocene carboxamides with various allenes provided good yields ranging from 44 to 80% of substituted ferrocene [4+3] annulated azepines **3aa-3ad**. The carboxymethyl substituted ferrocene substrate afforded a moderate yield (40 and 73%) of annulated azepines products **3ae** and **3af** with unaltered diastereoselectivity (>20:1). It seems that the steric crowd on the second Cp ring slows down the reactivity as low yields (65% for **3aa** versus 92% for **3a** and 80% for **3ab** versus 95% of **3t**) were observed, and slightly longer reaction hours are needed for the reactions. To check the scalability, the developed reaction has been carried out at the gram scale for the preparation of diastereomers **3a** and **3f**.

Scheme 3. Substrate Scope for Kinetically Controlled Diastereomers



[a] Reaction conditions: same as in Scheme 2 at 25°C.

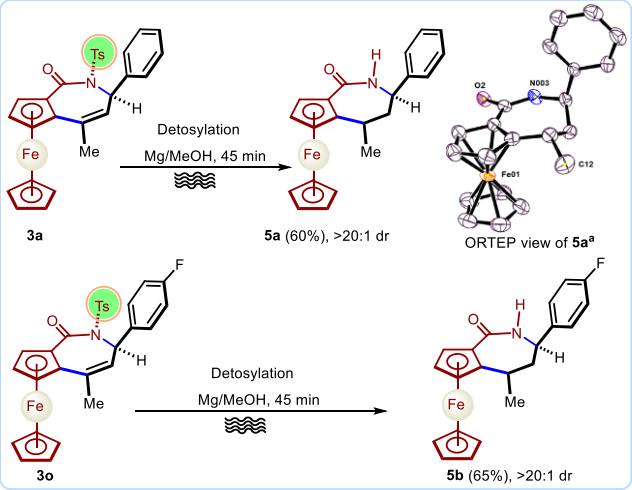
Indeed, nearly similar yields of 78 and 50% (versus 92 and 58%) with excellent *dr* were obtained for diastereomers **3a** and **3f**, respectively, suggesting the usefulness of the developed Rh-catalyzed [4+3] annulation reaction. Next, the substrate scope was explored for the preparation of substituted kinetically controlled diastereomers at room temperature (Scheme 3, Table 1,

entry 8). Benzylallene **2a** afforded a good yield (88%) of kinetically controlled diastereomer **4a** with an excellent *dr* (>20:1). Methyl substitution in the lower Cp ring of ferrocenecarboxamide **1b** led to a lower yield (55%) of the kinetically controlled [4+3] annulated diastereomer **4b**.

Similarly, an electron-donating *ortho*-methyl substituent in phenyl allene **2b**, electron-withdrawing *ortho*, *para*-dichloro, *ortho*-bromo, and *ortho*-fluoro and *meta*-chloro and *meta*-difluoro substituents in phenyl allenes resulted in a slight decrease in the yields (75% and 55-73%) of annulated azepines **4c-4i**, however, with an excellent diastereomeric ratio. The lower yields of the substituted kinetically controlled diastereomers **4b-4g** may be due to the steric effect. Similarly, heteroatom-substituted benzyloxy allene **2p** led to a moderate yield (65%) of **4j**, and also reduced diastereomeric ratio (>2.3:1) was realized (Scheme 3).

Further, ferrocene-fused azepines were modified by the removal of the *N*-tosyl group for a variety of late-stage transformations (Scheme 4). In our first attempt, the removal of the *N*-tosyl group by an established samarium iodide reagent[20] failed. Alternatively, Mg in CH_3OH has been applied for the detosylation under sonication conditions. To our delight, ferrocene azepines **3a** and **3o** not only underwent detosylation but also led to the reduction of alkene in an unprecedented manner to afford N-H containing tetrahydro ferrocene fused azepines **5a** and **5b** in 60% and 65% yields with intact diastereoselectivity (>20:1).

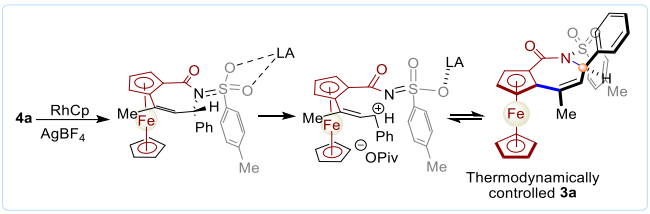
Scheme 4. Derivatization: Detosylation and Reduction of **3a** and **3o** for the Synthesis of Tetrahydro Azepine with intact *dr*



[a] ORTEP View of **5a** with 50% Ellipsoid Probability

To gain insight about temperature-dependent formation of both diastereomers **4a** and **3a**, several experiments on isolated kinetically controlled **3a** was carried out in the presence of Lewis acids (see SI, pages S36-S38). A combination of silver and rhodium salts offers full conversion into thermodynamically controlled diastereomer **3a** to our delight. Based on the control experiments on kinetically controlled diastereomer and DFT computation (SI, Table S10, page S172), it seems, the kinetic-controlled diastereomer **4a** could isomerize into the thermodynamic-controlled product **3a** via Rh-promoted and Lewis acid (LA)-mediated thermal isomerization (Scheme 5). Sulfonyl group of azepine **4a** interacts with Lewis acids (RhCp, $AgBF_4$), which could facilitate the ring opening[20] to form an allylic type of cationic intermediate. Ultimately, allylic type intermediate may proceed for intramolecular ring closing by the addition of nitrogen from the less hindered side to furnish stable thermodynamically controlled [4+3] **3a**.

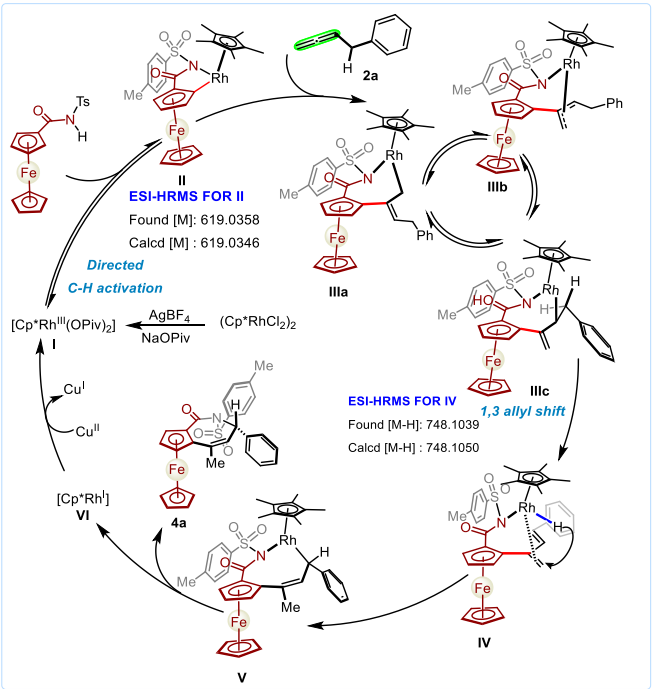
Scheme 5. Rh-Promoted and Base Mediated Thermal Isomerization of Kinetically Controlled **4a** into Thermodynamically Controlled **3a**.



The energy difference between two diastereomers **3a** and **4a** is 6.27 kcal/mol (based on DFT computational studies).

Based on the control experiments and isotopic labeling studies (See SI, pages S36-S38) and DFT computation (*vide infra*), a tentative mechanism was proposed for Rh-catalyzed CH-activation for diastereodivergent synthesis of ferrocene-fused azepines (Scheme 6). The substitution of the acidic NH group of the substrate **1a** with OPiv ligand of *in-situ* formed $Cp^*RhIII(OPiv)_2$ **I** would afford Rh-amidate type of intermediate, followed by the activation of C-H bond *via* concerted metalation deprotonation (CMD) could generate rhodacycle **II**.

Scheme 6. Proposed Mechanism for Rh-Catalyzed [4+3] Annulation for the Formation of Kinetically Controlled Diastereomers



The mass values for intermediates **III** to **VI** are the same.

Further, the interaction of rhodacycle **II** with the benzylallene and subsequent migratory insertion of benzylallene into the Rh-C bond could generate σ-rhodium allylic species **IIIa**. This would transform into π-rhodium η^3-allylic rhodium **IIIb**, which may further isomerize to σ-rhodium allylic **IIIc** having Rh-C σ-bond adjacent to benzylic position.[18] The *in-situ* formation of rhodacycle **II** and intermediate **III** was also studied by mass spectrometry as observed masses for **II** and **III** were 619.0358 and 748.1039, respectively. *β*-H Elimination in **IIIC** could afford Rh(III) diene hydride species **IV** which upon hydride re-insertion afforded 8-membered σ-bonded rhodacycle **V**. This upon reductive elimination afforded the desired kinetically controlled ferrocene fused azepine **4a**. The heating of the kinetically controlled diastereomer **4a** under the optimized reaction conditions where silver and rhodium act as Lewis acid leads to complete conversion into thermodynamically controlled diastereomer **3a**. Here in our study, except for the seven-membered ring azepine, the formation of a five-membered [4+1]-isoindolinone ring was not observed.[21] The DFT computed ∠N-Rh-C angle (81.7°) for reductive elimination in 8-membered rhodacycle is shorter as compared to 6-membered rhodacycle (87.0°). This seems to favor the reductive elimination of the proposed 8-membered rhodacycle over the 6-membered rhodacycle. Next, the calculated energy of 6- and 8-membered rhodacycles indicated that the 6-membered rhodacycle is higher in energy than the 8-membered rhodacycle by 9.46 kcal/mol (SI, Table S9, pages S171-S172), consequently, the formation of 6-membered rhodacycle with pianostool geometry may be less favored.

In conclusion, we have developed for the first-time temperature-dependent diastereodivergent [4+3] regioselective intermolecular annulation of *N*-tosylferrocenecarboxamide with allenes. The developed C–H and C-N annulation reaction proceeded under mild conditions, showing a broad substrate scope with diverse functional group compatibility, which enabled a variety of novel ferrocene fused azepines. Further, by controlling the temperature, a series of kinetically and thermodynamically controlled diastereomers having point planar stereocenter has been prepared with excellent *dr*. The synthesized ferrocene fused azepines have also been derivatized and the tosyl group has been deprotected into the N-H group for late-stage transformation without erosion in *dr*. Additionally, we have shown that the allenes can be used for [4+3] annulation for the first time. Currently, efforts are being made to diversify the enantioselective C–H bond in arenes using an allenes coupling partner.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the Publications website.

Experimental details, crystal data, characterization data (PDF)

Accession Codes

CCDC 2285354, 2285355, and 2285356 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: + 44 1223 336033.

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Author Contributions

SK and RAT designed the research. RAT, DP, SJ, VC, BS, and KR synthesized all the precursors and ferrocene-fused azepines. All the mechanistic studies and controlled experiments were performed by RAT and DP. DFT computational studies were done by RJ. The manuscript was written through the contributions of all the authors and compiled by SK and RAT. All authors have given approval to the final version of the manuscript. ‡Batul Shakir and Komal Rohilla contributed equally.

Notes

Authors declare no conflict of interest.

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