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Highly diastereoselective Heck–Matsuda reaction with pyrazolyl diazonium salts†

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The Heck–Matsuda (HM) reaction is a powerful synthetic approach cut out for C–C bonds formation under mild conditions. We demonstrated that pyrazolyl diazonium salts are suitable reagents in this protocol, allowing us to deliver highly substituted cyclopentenols and cyclopentenamines with an excellent degree of diastereoselectivity and a control of enantioselectivity.

Functionalized 5-membered carbocycles represent a valuable and versatile chemical motif since they are widespread in natural and pharmaceutical compounds.[1] Substituted cyclopentene scaffolds with controlled, defined stereochemistry could be envisaged as synthetically rewarding building blocks, despite their challenging preparation.[2] In our group, we recognized substituted 4-(pyrazol-4-yl)cyclopent-2-en-1-ols and 4-(pyrazol-4-yl)cyclopent-2-en-1-amines as advanced, chemically tractable building blocks to achieve high complexity molecules with well-defined stereochemistry (Fig. 1).

These scaffolds offer reactive moieties such as the allylic hydroxyl/amino functionalities, which can undergo conventional chemical transformations through essential reactions.[3] Ultimately, the possibility of inserting a diversely substituted pyrazole onto the cyclopentenyl scaffold makes the resulting compounds of broad interest, as the pyrazole is a valuable heterocycle frequently found in biologically active compounds and a key structural unit crucial in the modern medicinal chemistry portfolio.[4,5] Although the C-4 position of these heterocycles is the most nucleophilic, allowing direct cross-coupling modifications *via* C–H activation,[6] the insertion of a functionalized cycloaliphatic portion onto this carbon atom has not yet been fully disclosed.

Taking into account the potential, broad applications of substituted 4-pyrazolyl-1-cyclopenten-amines/-ols, we embarked on this challenging synthetic goal by exploiting a classical palladium-catalysed approach. Due to its versatility and compatibility with several functional groups, we envisaged that the Heck reaction could be a suitable tool to address our synthetic objective.[7] Although the development of the Heck reaction dates back to 1968,[8] this approach and its variations still represent a powerful tool to functionalize olefins in synthesizing both natural and pharmaceutical compounds.[7] In addition to bromides and iodides, several pseudohalides can react as coupling reagents offering alternatives to installing the new C–C bond. Matsuda and co-workers[9] demonstrated that aryl diazonium salts could react under mild palladium-catalysed conditions offering many valuable advantages. This synthetic variation, named Heck–Matsuda (HM) reaction, works without structurally complex ligands, under relatively mild conditions, and with high levels of regio- and stereo- control in the final products.[10] Although phenyl-based diazonium salts are considered strategic reagents to achieve complex compounds, the preparation of the corresponding heteroaryl analogs and their application[11] in palladium-catalysed coupling reactions have received limited attention.[12]

Herein, we describe the synthesis of a series of 4-diazonium pyrazolyl tetrafluoroborate salts **1** and their application in a highly stereoselective HM reaction. Based on the previously reported data using phenyl-diazonium salts,[13] cyclopent-3-en-1-ol (**4**) was selected as a benchmark olefin, which allowed affording

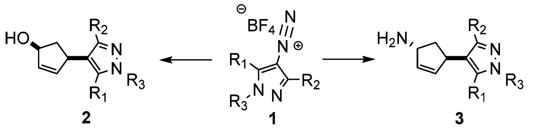

Fig. 1 From pyrazolyl diazonium salts to highly substituted cyclopentenyl derivatives.

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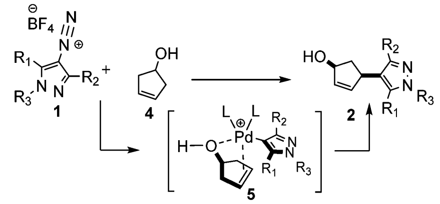
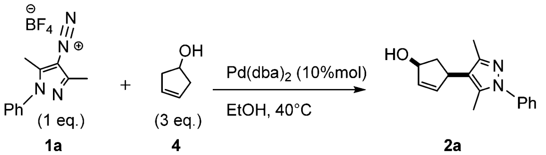
† Electronic supplementary information (ESI) available: Experimental procedures for intermediates and final compounds' synthesis, complete characterization data and copies of ^{1}H, ^{13}C, COSY, HSQC and ^{19}F NMR spectra (pdf) of compounds **1a–n**, **2a–n**, **3b,l** and **S16**, chiral HPLC analyses of racemic and enantio-enriched compound **2l**, TGA analysis of salts **1a,d,f,i,k-m**. See DOI: https://doi.org/10.1039/d3nj01724a



Scheme 1 Outcome and proposed mechanism of the HM reaction with pyrazolyl diazonium tetrafluoroborate salts **1**.

Table 1 Optimization of HM reaction with pyrazolyl diazonium salt **1**



Entry	Solvent	Catalyst (%mol)	T (°C)	Time (h)	Yield[a]	dr[b]
1	DCM[c]	$Pd(dba)_2$ (5%)	r.t.	1	< 5%	—
2	MeCN[c]	$Pd(dba)_2$ (5%)	r.t.	1	< 5%	—
3	EtOH	$Pd(dba)_2$ (10%)	60	0.5	50%	98.8 : 1.2
4	EtOH	$Pd(dba)_2$ (10%)	40	3	53%	99.4 : 0.6
5	EtOH	$Pd(dba)_2$ (10%)	r.t.	24	25%	99.6 : 0.4
6	EtOH	$Pd(dba)_2$ (5%)	40	7	32%	—
7	EtOH[d]	$Pd(dba)_2$ (10%)	40	6	31%	—
8	EtOH	$Pd_2(dba)_3$ (10%)	40	4	39%	97.9 : 2.1
9	EtOH	$Pd(OAc)_2$ (10%)	40	8	30%	99.9 : 0.1
10	MeOH	$Pd(dba)_2$ (10%)	40	2	38%	97.0 : 3.0
11	iPrOH	$Pd(dba)_2$ (10%)	40	28	17%	98.1 : 1.9
12	MeCN	$Pd(dba)_2$ (10%)	40	24	—	—
13	EtOH[e]	$Pd(dba)_2$ (10%)	40	3.5	50%	99.3 : 0.7
14	EtOH[f]	$Pd(dba)_2$ (10%)	40	3.5	54%	99.2 : 0.8

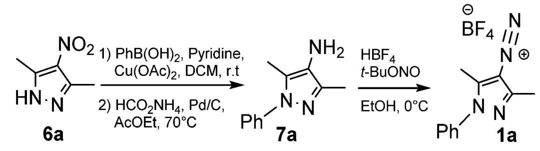
[a] Isolated yield. [b] dr: diastereomeric ratio, calculated by UPLC-MS analysis for *cis*-isomer. [c] **4** (2 eq.) and NaOAc (3 eq.). [d] **4** (1.5 eq.). [e] $CaCO_3$ (1.1 eq.) was added. [f] 2,6-di-*tert*-butyl-4-methylpyridine (1.1 eq.) was added.

substituted 4-(pyrazol-4-yl)cyclopent-2-en-1-ol derivatives **2** with a high degree of *cis*-stereocontrol (Scheme 1).

To achieve this aim, we prepared our model substrate **1a** by a three-step synthesis starting from commercial 3,5-dimethyl-4-nitro pyrazole (**6a**) (Scheme 2). The desired 1-phenyl-4-amino-3,5-dimethyl pyrazole (**7a**) was produced in excellent overall yield (90%) by sequentially applying a standard Chan–Lam protocol to insert the phenyl moiety in position *N*-1 of the pyrazole, followed by nitro group reduction using ammonium formate in the presence of Pd/C. Following classical conditions, the amino group of **7a** was converted into the stable diazonium salt **1a** in good yield (80%).

With diazonium salt **1a** in hand, to explore the feasibility and versatility of this synthetic approach, we began our investigation by carefully screening a few conditions and experimental parameters. We first monitored the scope of this protocol applying conditions previously reported in the work of Matsuda.[9] We explored a few changes, such as the temperature, the solvent, and the palladium species. However, these initial attempts provided only traces of the desired product **2a**, as a consequence of a fast diazonium salt decomposition promoted by sodium acetate (NaOAc) as a mild base (Table 1, entries 1 and 2). To avoid this undesired side-reaction we then focused on developing a base-free protocol. This strategy led to the expected coupling product **2a** (Table 1, entry 3) when the reaction was conducted in EtOH at 60 °C and in the presence of 10% of $Pd(dba)_2$. The HM product **2a** turned out to be a mixture of the *cis*- and *trans*-diastereoisomers, with the *cis*-isomer as the major component (dr = 98.8 : 1.2). The relative configuration of the major *cis*-isomer was assigned by analysing the ^1H-NMR spectra of similar stereoisomers reported in the literature[13] and of the corresponding *trans*-stereoisomer obtained after Mitsunobu reaction (see the ESI†). These findings are in line with the prediction of a model where electrostatic non-covalent interactions occur in the coordination complex **5** (Scheme 1), as proposed in previous studies.[13]

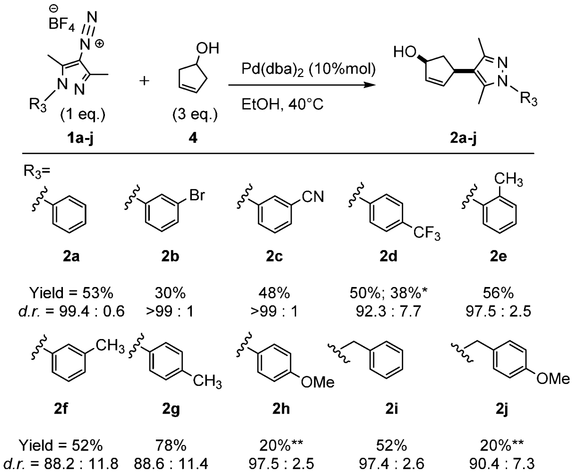
While lowering the temperature from 60 °C to 40 °C increased the reaction time (from 30 minutes to 3 h), marginally affecting the yield and the diastereoselectivity (entry 4), carrying out the reaction at room temperature resulted only in partial conversion after one day (entry 5). The reduction in the amount of either the catalyst (5% mol) or the olefin (1.5 eq.) drastically decreased the overall yield (32% and 31%, respectively; entries 6 and 7). Replacing the initially identified catalyst with $Pd_2(dba)_3$ or $Pd(OAc)_2$ led to lower yields and longer times in both cases, although with slightly higher diastereomeric ratio for the diacetate salt (entries 8 and 9).



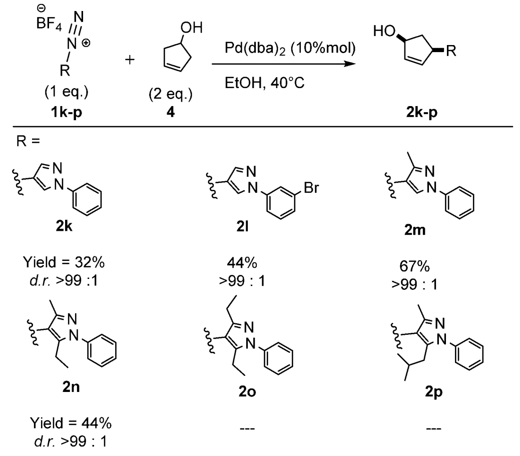
Scheme 2 Synthesis of diazonium salt **1a**.

The effect of the solvent on both the overall yield and stereochemical outcome was also investigated. While MeOH led to a faster reaction (*ca.* 2 h) but with a significant formation (*ca.* 25%) of a side-product (entry 10), the use of either *i*PrOH or MeCN resulted in poor or no reactivity (Table 1, entries 11 and 12). Finally, the effect of different types of bases was evaluated. $CaCO_3$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) were selected to explore whether the heteroaryl diazonium salt **1a** could efficiently react in their presence. However, they turned out to be ineffective, as the overall outcome was similar to the base-free conditions (entries 13 and 14). Although still preliminary, the use of $Pd(dba)_2$ (10% mol) in EtOH at 40 °C (Table 1, entry 4) was chosen as the benchmark reaction conditions, being a good compromise between overall yield, dr, and versatility. Having set the parameters suited to exploit pyrazolyl diazonium salts in the HM approach, we focused on studying the scope of this methodology.

Firstly, we synthesized a few *N*-substituted 3,5-dimethyl-pyrazolyl diazonium salts **1b–j** (see the ESI†) in a similar manner as reported for **1a** (Scheme 2). Interestingly, we observed that all these compounds showed good chemical stability, allowing simple isolation and storage without losing their reactivity. The thermal stability of some pyrazolyl diazonium tetrafluoroborates was also assessed by TGA analyses, showing for all of them a high



Scheme 3 Effect of *N*-substitution of pyrazolyl-diazonium salts in the HM reaction. * One-pot protocol; ** DTBMP (1.1 eq.) was added.



Scheme 4 Heck–Matsuda with substituted *N*-phenyl-pyrazolyl diazonium salts.

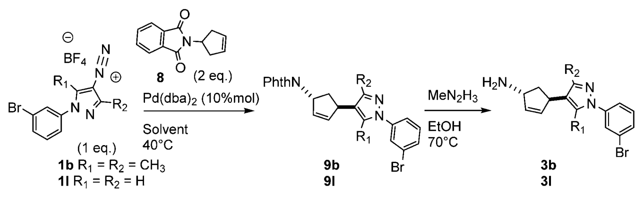
degree of stability (see the ESI†). Using the optimized conditions, we challenged salts **1b–j** in our synthetic protocol (Scheme 3). Diazonium salts **1b–d** bearing electron-withdrawing groups on the aryl gave slightly lower yields (30–50%) compared to the unsubstituted phenyl analog **1a**, probably due to their higher susceptibility to de-diazotization under these conditions. Compound **1d** was also tested in a one-pot protocol (diazotization/HM reaction, see the ESI†) providing the corresponding cyclopentenol **2d** in an overall acceptable yield. The presence of a methyl substituent in *ortho*, *metha*, or *para* position of diazonium salts **1e–g** resulted in the corresponding products **2e–g** in good to high yields. The 78% yield observed for the *para*-methyl phenyl analog **2g** suggests a possible steric effect of the substituent on the phenyl ring in the reactive Pd-complex. The electron-donating *p*-methoxy group, as in diazonium salt **1h**, led to poor yield. To expand the scope of this approach, we investigated benzylic groups as *N*-substituent of the pyrazole, introducing a benzyl and a *p*-methoxy benzyl functionality (**1i,j**); they gave similar results to their aryl analogs **1a,h**, affording cyclopentenols **2i,j** with comparable yields. Unfortunately, attempting to use either unsubstituted (*R*$_3$ = H) or tosyl (*R*$_3$ = *p*-tolylsulfonyl) substituted pyrazoles resulted in no or low reactivity, probably due to the formation of an unreactive complex of the reactive species with the palladium.[14]

We then prepared a series of unsubstituted, symmetrical, and unsymmetrical alkyl-substituted *N*-phenyl-pyrazolyl diazonium salts **1k–p** to potentially unveil and verify the effects of the substituents at 3- and 5-position of the pyrazole on the yield and the stereochemical outcome (Scheme 4).

In our optimized HM reaction conditions, 3,5-unsubstituted pyrazolyl diazonium tetrafluoroborates **1k,l** led to complete conversion in short times (*ca.* 1.5–2h), delivering the desired products **2k,l** in moderate to good yields and nearly complete *cis*-stereoselectivity. Although this protocol led to the desired cyclopentenol **2k** in an acceptable 32% yield, by using diazonium salt **1k** we also isolated a by-product (*ca.* 10% isolated yield) not detected in the previously investigated cases (see compound **S16**, the ESI†).[15] Unsymmetrical pyrazolyl-diazonium salts **1m,n** worked nicely, giving the corresponding substituted cyclopentenols **2m** and **2n** in good yields (67% and 43%, respectively) and high *cis*-stereoselectivity. Unfortunately, when testing hindered analogs, such as the 3,5-diethyl- (**1o**) or the 5-isobutyl-3-methyl (**1p**) substituted pyrazolyl diazonium salts, many decomposition products were observed with only trace amounts of the desired products detected in the crude mixture. Finally, to assess the robustness and efficiency of our protocol, we tested the reaction of cyclopent-3-en-1-ol (**4**) with bromo-phenyl diazonium salt **1b** at a gram-scale, affording **2b** with high *cis*-diastreoselectivity in moderate yield, similarly to the milligram-scale reaction (see the ESI†).

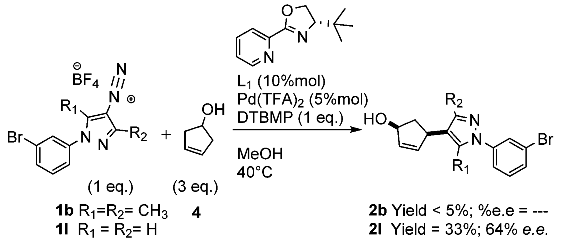
Having assessed the conditions to use pyrazolyl diazonium salts in the HM protocol for the highly diastereoselective synthesis of substituted cyclopentenols, we decided to broaden the scope of this approach to afford the corresponding cyclopentenamines **3** (Table 2). We initially aimed to prepare *cis* isomer **3b** through a concise and elegant approach by applying the HM reaction conditions used to produce cyclopentene **2b**. In the first attempt, HM product **9b** was afforded as a mixture of diastereoisomers with the *cis* isomer as major component

Table 2 HM reaction applied to the synthesis of substituted 4-(pyrazol-4-yl)cyclopent-2-en-1-amines **3b,l**



Entry	Cmpd	Solvent	Time (h)	Yield (**9**/**3**)[a]	Dr (**9**)[b]
1	**1b**	EtOH	20	23%/98%	77 : 23
2	**1b**	DMA	4	50%/97%	25 : 55
3	**1b**	MeCN/H$_2$O (1 : 1)	20	21%/98%	<1 : 99
4	**1l**	MeCN/H$_2$O (1 : 1)	5	50%/98%	<1 : 99

[a] Isolated yields. [b] Dr: diastereomeric ratio, *cis:trans* ratio calculated by ^{1}H NMR analysis.



Scheme 5 Enantioselective HM reaction with substituted pyrazolyl diazonium salts **1b,l**.

(dr = 77 : 23, Table 2, entry 1). We then tested other solvents compatible with a base-free reaction protocol (*e.g.*, DMA and $MeCN/H_2O$). Notably, while DMA led to a diastereomeric mixture with the *trans* isomer as major component, the use of $MeCN/H_2O$ (1 : 1) gave the phthalimido-protected derivative **9b** with complete inversion of stereochemistry (*cis:trans* dr $< 1:99$) (Table 2, entries 2 and 3). The corresponding cyclopentenamine **3b** was afforded in a straightforward and quantitative manner by deprotection of **9b** with methylhydrazine in EtOH.

To unambiguously confirm the stereochemistry of *trans* cyclopent-2-en-1-amine **3b**, we converted *cis*-cyclopentenol **2b** into the corresponding *trans* isomer by a simple Mitsunobu reaction using phathalimide, followed by methylhydrazine deprotection (see the ESI†). In a similar manner, by using unsubstituted *N*-bromophenyl-pyrazolyl diazonium salt **1l**, *trans*-cyclopentenamine **3l** was afforded in an acceptable yield (49% over two-steps) with complete diastereocontrol (Table 2, entry 4).

As concluding experiments, we decided to preliminary challenge our Pd-catalysed heteroaryl HM protocol in the presence of a chiral ligand to investigate whether our pyrazolyl diazonium salts could react under a stereoselective control, delivering the desired products with induction of enantioselectivity. As initial experiments, we reproduced the conditions where PyBOX and PyOX, as chiral ligands, were successfully applied in a HM protocol using phenyl diazonium salts.[13,16] Remarkably, whereas the dimethyl pyrazole derivative **1b** reacted poorly in the presence of selected chiral ligands, *cis*-stereoisomer **2l** was exclusively obtained using ligand **L1** in an acceptable yield (33%) and a promising enantiomeric excess (64% e.e.) (Scheme 5, see also the ESI†). Although still very preliminary, these findings suggest that an enantioselective induction could be obtained with heteroaryl diazonium salts, affording the final products with control of both diastereo- and enantioselectivity.

In conclusion, we demonstrated that 4-diazonium pyrazole salts are suitable reagents for the Pd-catalysed HM reaction. They have been found to stereoselectively provide either 1,4-disubstituted *cis*-cyclopentenols or 1,4-disubstituted *trans*-cyclopentenamines, as key synthetic intermediates. Although the current work may well be at a preliminary stage, we envisaged that it could represent an adequate protocol allowing the synthesis of highly substituted heterocyclic compounds, with potential use in medicinal chemistry and chemical biology. Further developments, primarily targeting increased overall yields and enantioselectivity may provide valuable insights on how to expand the scope and the stereochemical outcome of this approach. The ambition of the present work is mainly to stimulate further investigations of these marginally explored heteroaryl reactive species in other metal-catalysed coupling reactions to achieve complex molecular architectures.

Conflicts of interest

There are no conflicts to declare.

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