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Optimizing the Mizoroki–Heck reaction of cyclic allyl amines: Gram-scale synthesis of preclamol without protecting groups

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ABSTRACT

Though a widely used metal-catalyzed cross-coupling process, the Mizoroki–Heck (MH) reaction can be a capricious transformation. This is particularly true for oxidation-prone alkene substrates containing ligating heteroatoms, as in the case of N-alkyl tetrahydropyridines, whose MH reactions have been underexplored due to the many side reactions that hamper the process. Since the products of tetrahydropyridine Heck reactions are direct precursors to potent pharmacophores, and therefore of commercial value, this is a significant drawback. We report here the results of our study designed to deliver an optimized, scalable MH procedure for N-alkyltetrahydropyridines and its exemplification in a gram-scale synthesis of the drug substance preclamol.

1. Introduction

Among the many catalytic processes available to the modern synthetic chemist, the Mizoroki–Heck (MH) reaction [1] is of special significance as the first reported method [2] that enabled direct, substoichiometric catalytic modification of simple alkenes: The overall transformation is effectively a CH activation process, in which an aryl unit is inserted into an sp^2 CH bond. The reaction has been intensely studied and optimized, and a wide range of coupling partners (aryl halides, triflates, sulfonates, diazonium salts, iodonium salts), alkenes, and catalysts have been used productively in the process, with many successful applications to the production of complex natural and synthetic targets [3]. Notwithstanding the proven synthetic power of the transformation, there are several known limitations on the process; thus, the reactions are often heterogeneous (precluding detailed kinetic and mechanistic analysis), and some alkene classes are unreliable and capricious substrates. Unsaturated amines fall into this category, often undergoing inefficient transformations that require high substrate or catalyst loading; this is especially the case for cyclic allylamines (such as tetrahydropyridines [4] and pyrrolines [5]), which react efficiently only if the lone pair of electrons on nitrogen is delocalized into an electron-withdrawing protecting group. This limitation is a particular drawback, since the method in theory allows direct synthesis of N-alkyl piperidines and pyrrolidines, a class of heterocycles with privileged pharmacological status, particularly in CNS-active compounds such as the marketed drugs paroxetine [6] and niraparib [7] (Fig. 1); however, to date, the limitations of MH reaction of tetrahydropyridines (lack of regioselectivity, overreaction, multiple isomerization pathways, and low yields) have severely restricted the use of this potentially impactful catalytic process.

3-Arylpiperidines are a class of heterocycles with particular biological potency, and preclamol (**1**) [8] occupies a preeminent position as a first-in-class antipsychotic drug substance. The compound is a dopamine autoreceptor agonist, and it has been used in human beings for the treatment of schizophrenia [9]. To produce this compound and other related biologically active compounds, a range of heterocycles can function as chemical feedstocks for catalytic processing (Fig. 2).

Thus, several catalytic methods using pyridines as feedstocks have been used to produce the preclamol core (Fig. 2a), including nickel-catalyzed Kumada [10] and Suzuki–Miyaura coupling [11,12] of 3-bromopyridine and pyridine C—H activation [13]. In these reactions, further nontrivial steps (alkylation, reduction,

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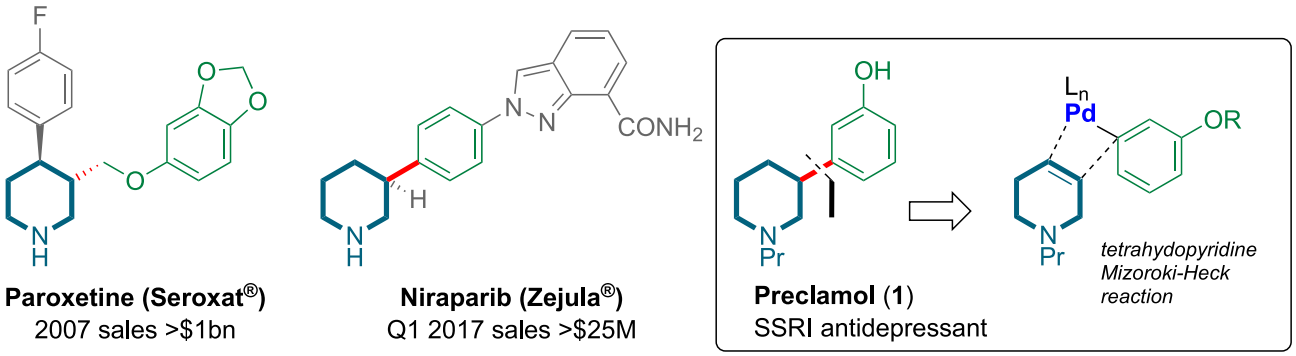


Fig. 1. Arylpiperidines: privileged biological motifs accessible from tetrahydropyridines.

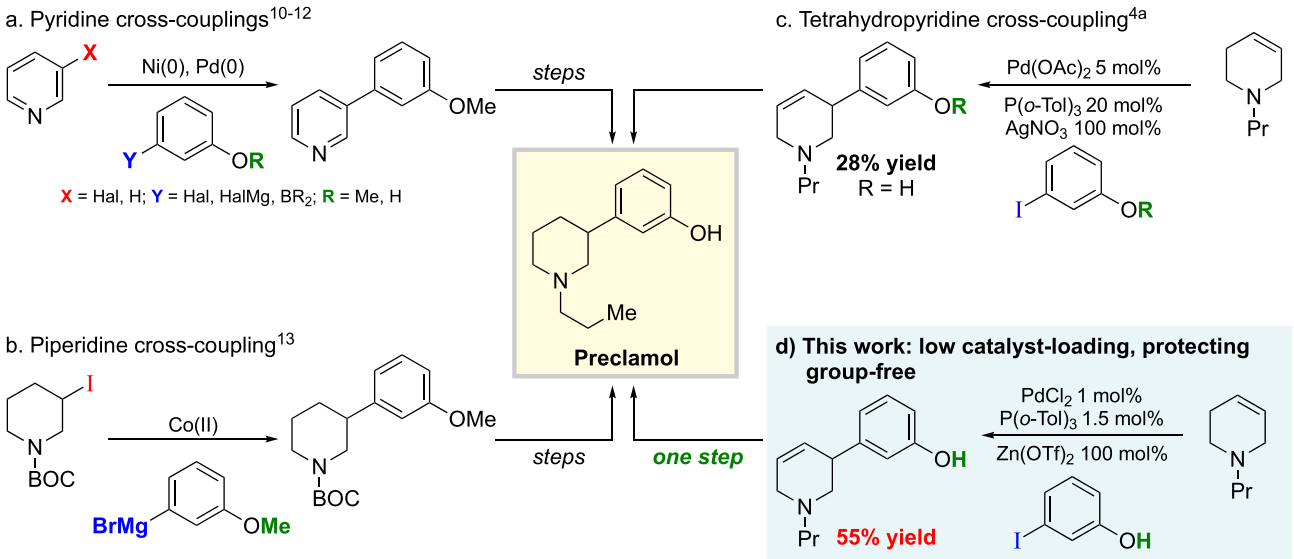


Fig. 2. Catalytic strategies for the synthesis of preclamol.

etc.) are needed to access the biologically active products. Cross coupling of nonaromatic amines has been less widely used to access the 3-arylpiperidine core, with the Co(II)-catalyzed coupling of 3-iodo-N-Boc-piperidine with Grignard reagents a notable example of such a strategy (Fig. 2b) [14]. In theory, the use of tetrahydropyridines (available in bulk from commercial sources) in an MH reaction would allow highly efficient access to 3-aryl piperidines, and the method has been used by Hallberg et al. to produce preclamol (Fig. 2c) [4a]. However, the method reported by these authors delivered the target 3-arylpiperidine inefficiently and required high ligand loading and stoichiometric Ag(I) as an additive [15]. Since this pioneering report, there have been no reports of MH reactions of alkyl tetrahydropyridines, which is likely a reflection of the poor yields obtained in these transformations, presumably due to the tendency of N-alkyltetrahydropyridines to undergo palladium-catalyzed side reactions (such as aromatization, giving pyridiniums) under the heterogeneous reaction conditions. Though in theory N-alkyl-3-arylpiperidines 2 (Fig. 3) are available via MH reaction of N-acyl tetrahydropyridines, in practice this is difficult, as shown by the work of Correia et al. [5b], due to the tendency for these reactions to deliver mixtures of enamines (isolated as hydrated products 3 and 4), which limits the utility of the reactions.

Given the ready commercial availability of N-alkyl tetrahydropyridines and the great utility of 3-arylpiperidines, we undertook a study of the factors affecting these complex MH reactions, and we report an improved and simplified synthesis of preclamol using our new method.

2. Materials and methods

Full experimental details and key spectra for products can be found in the Supplementary Material.

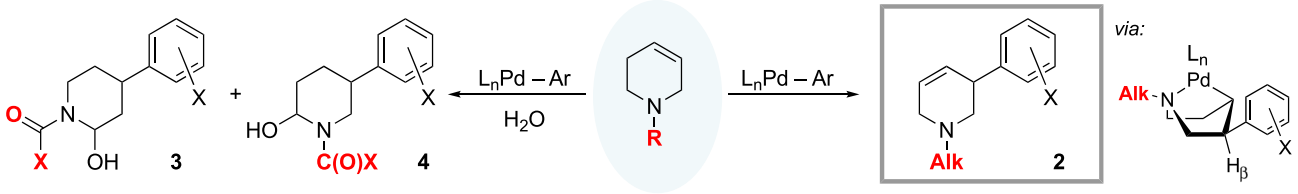


Fig. 3. Regiochemical divergence in MH reactions of tetrahydropyridines.

3. Results and discussion

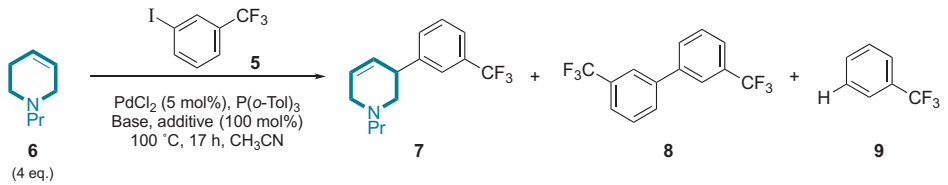
Our project had three key aims: first, to reduce the catalyst loading for the MH reaction to ≤1 mol.%; second, to avoid the use of a silver additive; third, to develop a method involving no protecting groups. In particular, the last goal was a demanding one, due to the known challenges in using phenols in palladium-catalyzed reactions [16], but was one that offered significant mass balance advantages if successful.

Preliminary studies of the N-alkyl THPy MH reaction confirmed the limitations of the reaction: the heterogeneous process delivered a multitude of products in addition to the desired arylated target, predominantly pyridinium species (and derived compounds) arising from metal-catalyzed oxidation. We therefore embarked upon a detailed analysis of the parameters of this reaction (Pd catalyst, ligand, base, solvent, additive, temperature). To simplify the analysis of this complex reaction, we chose (3-iodo)-benzotrifluoride, 5, as a model substrate, using ^{19}F NMR spectroscopy to study its reaction with N-propyltetrahydropyridine, 6. In this manner, we hoped to optimize the yield of the target product, 7, and quickly identify and quantitatively estimate the side-product profile of the reaction, thus giving valuable insights into the reaction mechanism and facilitating optimization. A summary of the salient data obtained from the initial optimization phase is given in Table 1. It thus became clear that silver(I) is not an essential additive (entries 7–12) and that use of an amine base was important for improving conversion of the substrate (entries 5–12).

The next phase of optimization was focused on improving the efficiency of the transformation by reducing the loadings of catalyst and substrate, and on the reaction temperature (Table 2).

Satisfyingly, the use of 1 mol.% $PdCl_2$ was effective without reducing the yield of 7 (Table 2, entry 3), though a 0.5% catalyst loading was less efficient (Table 2, entry 2). Variation in the stoichiometry of tetrahydropyridine had a less pronounced effect on the reaction, with a 50% decrease in loading having little negative impact on the yield of 7 (Table 2, entry 5). Finally, lowering the temperature to 70 °C proved to have a positive effect on the yield (Table 2, entries 7 and 8).

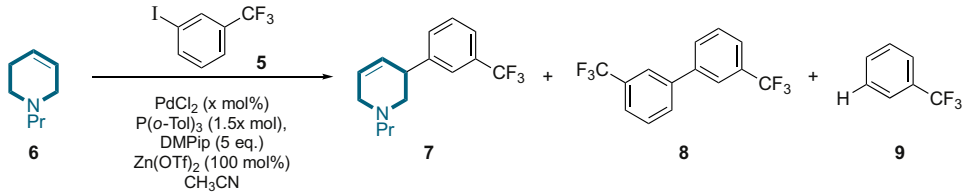
Table 1
Initial optimization of the MH reaction of tetrahydropyridine.



Entry	P(*o*-Tol)$_3$/mol.%	Base	Additive	Conversion/%	Yield/%		
					7	8	9
1	20	–	$AgNO_3$	100	18[a]	16	62
2	40	–	$AgNO_3$	100	10	9	78
3	10	–	$AgNO_3$	100	27	10	49
4	5	–	$AgNO_3$	100	35	11	42
5	5	DMPip (5 eq.)[b]	$AgNO_3$	92	39	3	16
6	5	DMPip (1 eq.)	AgOTf	100	49	7	19
7	5	DMPip (5 eq.)	$Cu(OTf)_2$	100	55	3	6
8	7.5	DMPip (1 eq.)	$Cu(OTf)_2$	100	59	3	11
9	5	DMPip (1 eq.)	$Cu(OTf)_2$	100	58	2	8
10	7.5	DMPip (1 eq.)	$(CuOTf)_2 \bullet PhCH_3$	98	58	4	12
11	7.5	DMPip (1 eq.)	$Zn(OTf)_2$	100	52	2	28
12	7.5	DMPip (5 eq.)	$Zn(OTf)_2$	100	61	2	10

[a] Yields estimated from ^{19}F NMR spectra.
[b] N,N-dimethylpiperazine.

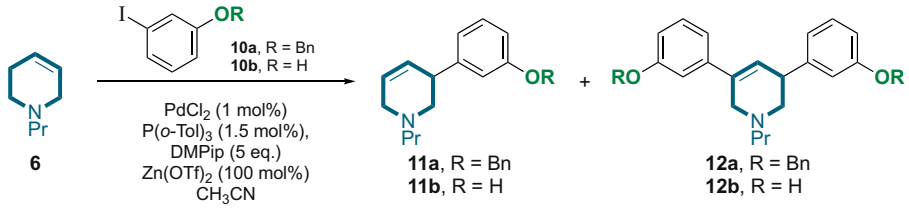
Table 2
Optimization of MH reaction of 6: influence of temperature, catalyst loading and stoichiometry.



Entry	$PdCl_2$/mol%	5/eq.	Temperature (°C)	Time (h)	Conversion	Yield/%		
						7	8	9
1	5	4	100	17	100	61[a]	2	10
2	0.5	4	100	17	95	56	2	10
3	1	4	100	17	100	60	1	9
4	5	3	100	17	100	63	2	9
5	5	2	100	17	100	59	3	8
6	5	1.5	100	17	100	56	4	8
7	1	3	70	120	100	67	1	6
8	1	2	70	120	100	62 (55)[b]	2	6
9	1	1.5	70	120	89	57	1	5

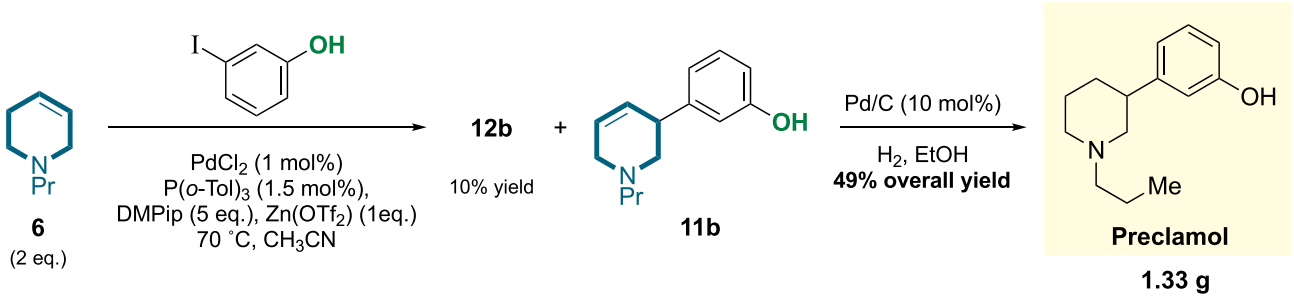
[a] Estimated from ^{19}F NMR spectra.
[b] Isolated yield (5 mmol scale reaction).

Table 3
Optimized MH reaction of 6.



Entry	6 (eq)	R	Yield 11/%	Yield 12/%
1	4	Bn	11a, 55[a]	12a, 5[b]
2	2	Bn	11a 49	12a, 13
3	4	H	11b, 55[c]	12b, 6
4	2	H	11b, 49	12b, 10

[a] Isolated yield, 5 mmol scale.
[b] Estimated from ^{1}H NMR.
[c] 12.5 mmol scale.



Scheme 1. Improved synthesis of Preclamol **1.**

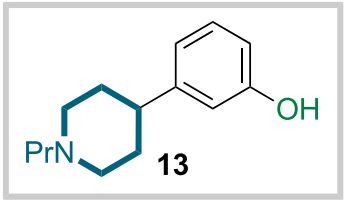


Fig. 4. Saturated amine 13.

Armed with an optimized procedure, we turned to the synthesis of preclamol, and observed that using either benzyl ether, 10a, or free phenol, 10b, MH reactions were significantly improved compared with the previously reported procedure.: in particular, 11b was obtained in 55% yield, compared with 28% reported by Hallberg et al. (Table 3, entry 3). In addition to the desired products, 11a and 11b, on the larger scale of these reactions, we now also detected the presence of novel diarylated alkenes, 12a and 12b.

When performed on a 12.5 mmol scale (Scheme 1), the extent of side reactions involved in MH reactions of N-alkyl tetrahydropyridines becomes apparent, with side products derived from other possible palladium σ -intermediates. Thus, in addition to 11b and diarylated amine 12b, preclamol (1) itself and saturated amine 13 (Fig. 4) were observed in small amounts, the latter products presumably formed via reductive MH processes [17]. Hydrogenation of either 11a or 11b gave preclamol in 49–55% overall yield.

4. Conclusions

In summary, we have designed and implemented an improved method for the MH reaction of N-propyltetrahydropyridine, which is more cost-effective, milder, and more functional-group-tolerant, and which efficiently provides access to gram quantities of preclamol in good overall yield. Developing an in-depth understanding of the detailed mechanistic features of this complex heterogeneous catalytic reaction is a focus of our current research.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jcat.2018.01.007.

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