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A rhodium-catalysed three-component reaction to access C1-substituted tetrahydroisoquinolines†

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A rhodium-catalyzed three-component reaction of diazo compounds, anilines and C,N-cyclic azomethine imines *via* trapping of transient ammonium ylides was developed. This reaction provided a simple and convenient approach for the synthesis of pharmaceutically intriguing tetrahydroisoquinoline derivatives in moderate to good yields (36–85%) with good diastereoselectivities (up to 95 : 5 dr) under mild reaction conditions.

Introduction

Tetrahydroisoquinolines (THIQs), especially C1-substituted tetrahydroisoquinolines, are important nitrogen-containing heterocycles widely spread in natural products and pharmaceuticals. These molecules exhibit many interesting biological properties,[1] ranging from inhibition of cancer cell proliferation and[1c] multiple cardiovascular activities related to different mechanisms of action,[1d–e] to anti-inflammatory,[1f] antimicrobial,[1g] and antiplasmodial activities,[1h] *etc*. For example (Fig. 1), praziquantel is a broad-spectrum antischistosomal agent[2] listed in the World Health Organization's List of Essential Medicines; lifitegrast is a novel integrin antagonist marketed in 2016 for the treatment of dry eye disease;[3] drug candidate BMS-962212 is a reversible, direct, and highly selective small molecule inhibitor of factor XIa in phase I clinical trials.[4] Considering the significant biological properties and potential clinical values of THIQ derivatives, the continued development of synthetic protocols for the efficient synthesis of these molecules is in high demand.

The structural modification of a preformed tetrahydroisoquinoline skeleton is a straightforward strategy to access multi-functionalized tetrahydroisoquinolines.[5] For example, cross-dehydrogenative coupling (CDC) reactions using readily available tetrahydroisoquinoline as the precursor could efficiently incorporate diverse functional groups into the C1-position of tetrahydroisoquinoline, but this approach generally requires stoichiometric external oxidants.[6] Recently, another valuable synthon, C,N-cyclic azomethine imine discovered by Tamura[7] and developed by Maruoka and co-workers,[8] has emerged as a versatile and promising architectural platform for the construction of various C1-substituted tetrahydroisoquinoline derivatives under mild conditions. Typically, C,N-cyclic azomethine imines serve as 1,3-dipoles to undergo a series of 1,3-dipolar cycloaddition reactions, including [3 + 2],[8,9] [3 + 3],[10] [4 + 3][11] and [5 + 1][12] cycloadditions, resulting in diverse tricyclic tetrahydroisoquinolines (Scheme 1a, path I). They also act as electrophiles to react with nucleophiles *via* nucleophilic addition to the C1-position rather than cycloadditions, but this is largely underdeveloped and the nucleophilic additions are restricted to the preformed traditional nucleophiles, *i.e.* terminal alkynes and isocyanides (Scheme 1a, path II).[13] Therefore, we are interested to know if the *in situ* generated

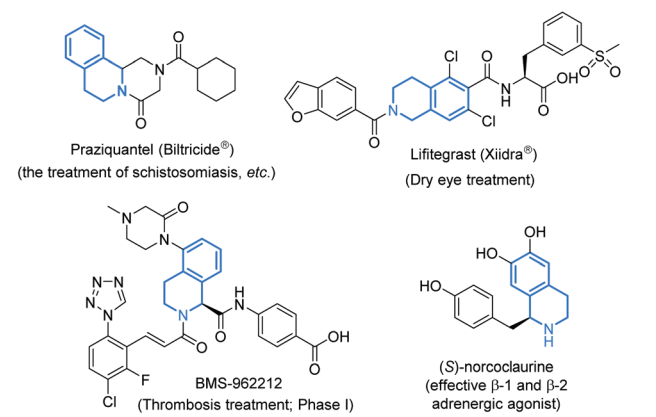

Fig. 1 Representative pharmacologically active compounds and natural products containing a tetrahydroisoquinoline moiety.

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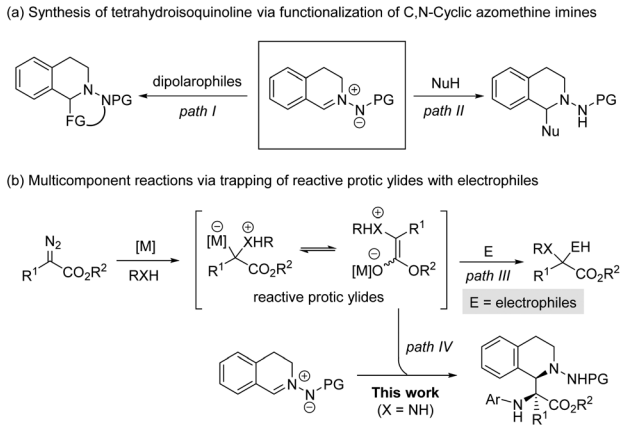


Scheme 1 Synthesis of tetrahydroisoquinoline derivatives using C,N-cyclic azomethine imines.

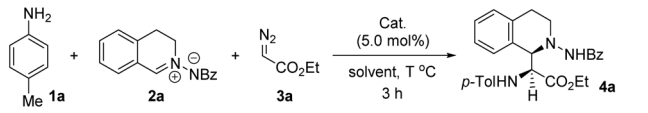
functionalized intermediates, such as nucleophilic transient ylides,[14] could be used as nucleophiles to undergo nucleophilic attack to C,N-cyclic azomethine imines at the C1-position, which will provide a new approach for the one-step synthesis of multifunctionalized tetrahydroisoquinolines.

In recent years, we have been developing novel multicomponent reactions *via* electrophilic trapping of protic ylide intermediates formed from carbenes and protic amino groups/hydroxyl groups (Scheme 1b, path III), which offer efficient protocols for the synthesis of structurally diverse compounds in an atom- and step-economic fashion under mild conditions.[14,15] This strategy is also applied to the derivatization of N-heterocycles, including dearomatization of N-activated pyridines and quinolines to achieve dihydropyridines and dihydro- and tetrahydroquinolines.[16] In view of the advantages of this intermediate-trapping process in the synthesis of N-heterocycles, we anticipated to employ it to produce tetrahydroisoquinoline derivatives using C,N-cyclic azomethine imines as the trapping reagents (Scheme 1b, path IV). It was envisioned that the reactive ylide generated from a diazo compound and an aniline could undergo nucleophilic addition to the C1-position of C,N-cyclic azomethine imines to obtain THIQs bearing an amino ester moiety. Herein we describe a unique three-component reaction of diazo compounds, anilines and C,N-cyclic azomethine imines allowing the efficient construction of tetrahydroisoquinoline derivatives.

Results and discussion

We began with the reaction of ethyl diazoacetate (**3a**) with *p*-toluidine (**1a**) and C,N-cyclic azomethine imine (**2a**) in CH_2Cl_2 at room temperature, in the presence of 5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$. Under these conditions, the desired trapping product **4a** was observed in a very low yield (Table 1, entry 1). We then turned to the widely used copper and silver catalysts, including $Cu(OTf)_2$, CuOTf, AgOTf, and CuI (entries 2–6), and the yield of **4a** was enhanced to 38% (entry 2). To our delight,

Table 1 Optimization of the reaction conditions for **1a**, **2a** and **3a**[a]

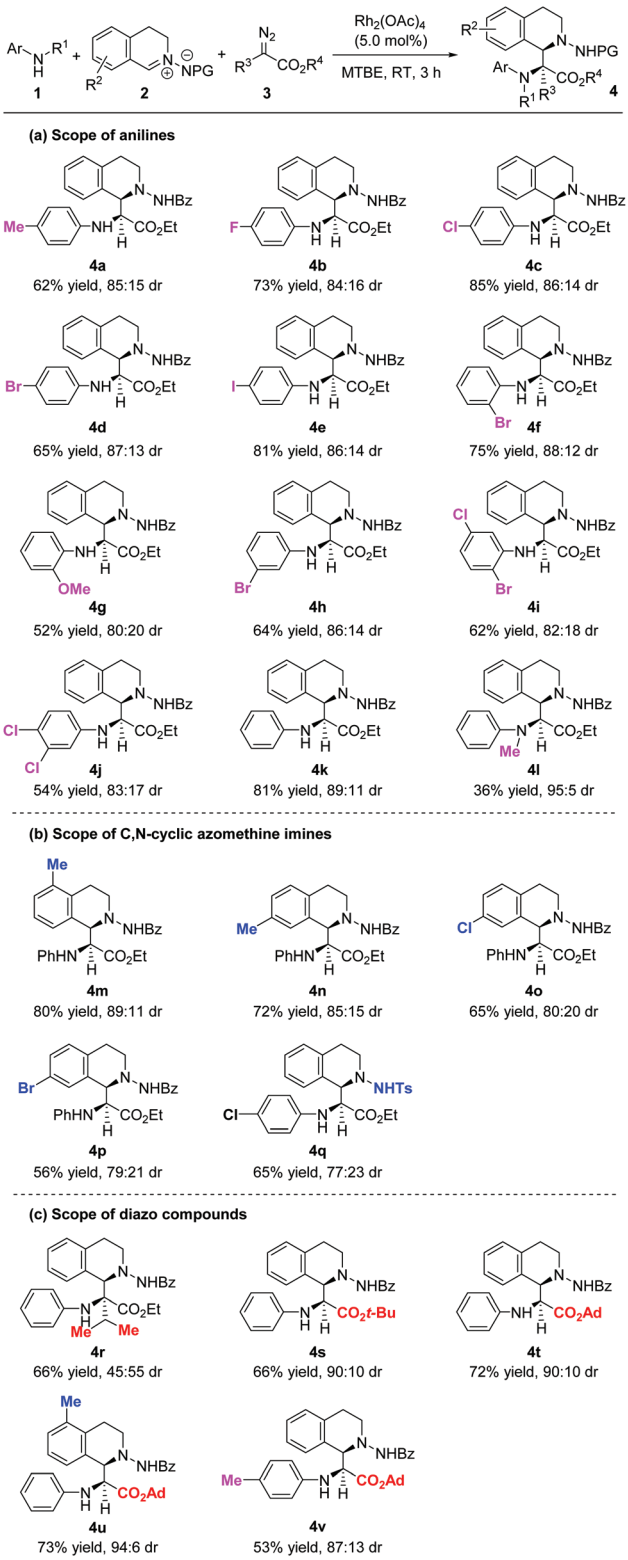


Entry	Cat.	Solvent	T/°C	Yield[b]/%	dr[c]
1	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	CH_2Cl_2	25	10	—
2	$Cu(OTf)_2$	CH_2Cl_2	25	38	79 : 21
3	CuOTf	CH_2Cl_2	25	23	74 : 26
4	AgOTf	CH_2Cl_2	25	5	—
5	CuI	CH_2Cl_2	25	9	—
6	$Rh_2(OAc)_4$	CH_2Cl_2	25	62	79 : 21
7	$Rh_2(OAc)_4$	$CHCl_3$	25	54	81 : 19
8	$Rh_2(OAc)_4$	DCE	25	46	74 : 26
9	$Rh_2(OAc)_4$	THF	25	58	83 : 17
10	$Rh_2(OAc)_4$	EA	25	42	79 : 21
11	$Rh_2(OAc)_4$	Toluene	25	57	82 : 18
12	**$Rh_2(OAc)_4$**	**MTBE**	**25**	**66 (62[d])**	**85 : 15**
13	$Rh_2(OAc)_4$	MTBE	10	26	85 : 15
14	$Rh_2(OAc)_4$	MTBE	45	69	81 : 19
15[e]	$Rh_2(OAc)_4$	MTBE	25	59	83 : 17

[a] Unless otherwise indicated, reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), **3a** (0.25 mmol), metal catalyst (5.0 mol%), solvent (2.0 mL), 3 h. [b] The yields were determined by crude ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] *syn*/*anti*; the diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Isolated yield. [e] 0.20 mmol **3a**. dr: diastereomeric ratio, DCE: dichloroethane, THF: tetrahydrofuran, EA: ethyl acetate, MTBE: methyl *tert*-butyl ether.

when $Rh_2(OAc)_4$ was used as a catalyst, the yield of **4a** was increased to 62% with 79 : 21 dr (entry 6). Subsequently, the solvent effect was investigated (entries 7–12), which revealed that methyl *tert*-butyl ether (MTBE) gave a slightly improved yield of 66% with 85 : 15 dr (entry 12). Having identified the catalyst and solvent, we continued to screen the reaction temperature (entries 13 and 14), in which lowering the temperature to 10 °C resulted in a reduced yield, and elevating temperature to 45 °C slightly increased the yield but decreased the dr value. Furthermore, reducing the loading of **3a** also diminished the yield of **4a** (entry 15). Therefore, the reaction conditions in entry 12 were identified as the optimal ones.

With the optimized reaction conditions in hand, the substrate scope of the three-component reaction was investigated and the results are summarized in Scheme 2. When different anilines containing one or two substituents at the phenyl group were assessed, the desired products **4a–4j** were achieved in moderate to good yields (52–85%) with good diastereoselectivities (up to 88 : 12 dr). Non-substituted aniline as a substrate gave the desired three-component product **4k** in 81% yield with 89 : 11 dr. Moreover, the use of *N*-methylaniline provided the desired product **4l** with high diastereoselectivity (95 : 5 dr), although the yield was modest (36%). As for the scope of C,N-cyclic azomethine imines, substrates with different substituents at the aromatic ring were tolerated, providing products **4m–4p** in similar yields (56–80%) with moderate to good dr values (up to 89 : 11). Furthermore, the N-Ts substituted azomethine imine was also effective to give the

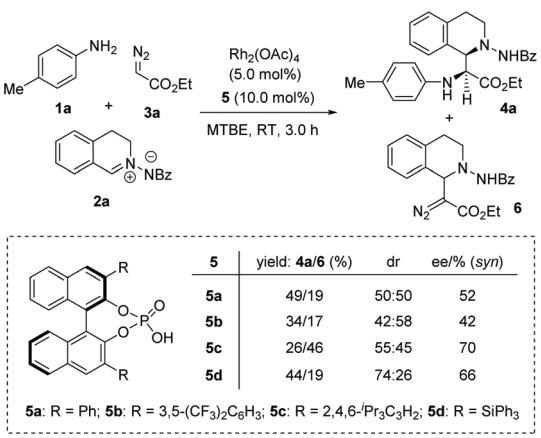


Scheme 2 Scope of a three-component reaction. Isolated yields are provided here. The dr value was obtained by ^{1}H NMR spectroscopy of the crude reaction mixture.

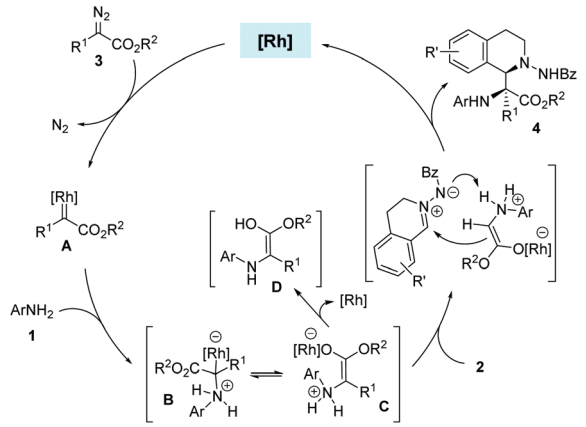
corresponding product **4q**. When evaluated with different diazo esters, the results showed that substrates with bulk ester groups, such as *tert*-butyl ester and adamantyl ester, could improve the diastereoselectivities of the reaction (90 : 10 dr) and have no deleterious effect on the yields (**4s–4t**), but an isopropyl attached to the diazo carbon would result in poor stereoselectivity (**4r**). Furthermore, the reactions examined with 1-adamantyl diazoacetate also gave rise to products **4u–4v** with good yields and diastereoselectivities. It is worth mentioning that aryl diazoacetates also resulted in the desired products, but a confirmed yield and dr value were not obtained due to the instability of the product *via* cleavage of the newly formed C–C bond during analysis and purification. Finally, the relative configuration of major products was determined to be *syn* by the X-ray single-crystal analysis of **4f**.[17]

We also investigated the asymmetric reaction using chiral phosphoric acids **5a–5d** as the chiral source.[18] As outlined in Scheme 3, in the presence of **5**, the ee value of *syn*-**4a** ranged from 42% to 70%, but low yields and poor diastereoselectivities were observed. The major side reaction is the direct addition of ethyl diazoacetate **3a** to **2a**, which was promoted by **5** and diminished the yield of the desired product **4a**. The highly selective asymmetric three-component synthesis remains challenging at the current stage, in which how to suppress the formation of **6** would be a key issue. Moreover, some chiral rhodium catalysts were also tested, but very low enantiomeric excess (<5%) was observed (see more details in the ESI†).

According to the control reactions (see the ESI†) and our previous studies on the trapping of ammonium ylides,[14,16b] a proposed reaction mechanism is illustrated in Scheme 4. Firstly, the rhodium-catalysed decomposition of diazo esters results in rhodium carbene **A**. The nucleophilic attack on **A** by anilines provides transient ammonium ylides **B** and the enolate form **C**. Trapping of these reactive intermediates with C,N-cyclic azomethine imines gives rise to C1-substituted tetrahydroisoquinoline derivatives and releases the rhodium catalyst. Alternatively, the non-metal associated enol **D** is also a possible intermediate involved in the process.[15d]



Scheme 3 Preliminary studies of asymmetric reactions.



Scheme 4 Proposed reaction mechanism.

Conclusions

In conclusion, we have developed a rhodium-catalysed three-component reaction of diazo compounds, anilines and C,N-cyclic azomethine imines, which proceeds through the trapping of transient ammonium ylides with C,N-cyclic azomethine imines. This study provides an efficient access to valuable functionalized tetrahydroisoquinoline derivatives in moderate to good yields (36–85%) with good to excellent diastereoselectivities (up to 95 : 5 dr) under very mild conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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