JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Highly Enantioselective Rhodium-Catalyzed [2+2+2] Cycloaddition of Diynes to Sulfonimines

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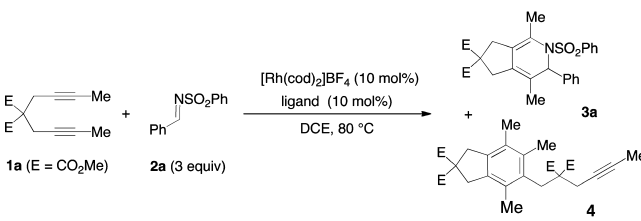
Supporting Information

ABSTRACT: A new asymmetric [2+2+2] cycloaddition of diynes to sulfonimines under rhodium catalysis that provides the corresponding enantioenriched 1,2-dihydropyridines in good yields is described.

The transition-metal-catalyzed [2+2+2] cycloaddition reaction is recognized as one of the most powerful and straightforward methods for the construction of polycyclic compounds.[1] There have been remarkable advances in terms of chemo-, regio-, and stereoselectivity in this reaction, so it has found many applications in the synthesis of complex molecules.[2] While access to various heterocyclic compounds is permitted through the [2+2+2] cycloaddition of diynes to C−heteroatom multiple bonds [nitriles, aldehydes, ketones, iso(thio)cyanates, etc.], the use of imines as unsaturated partners remains scarce. During their initial exploration of the rhodium-catalyzed aza-[5+2] cycloaddition of a cyclopropylimine to dimethyl fumarate, Wender et al.[3] reported the formation of a nondesired cycloadduct between two alkyne units and one imine. Ogoshi et al.[4] also described a related chemoselective transformation under nickel catalysis, yet with a restricted imine scope. Cyclizations between imines bearing a directing *N*-pyridyl group and two alkynes that are believed to involve [2+2+2] cycloaddition have also been reported.[5] To the best of our knowledge, these three reports are the only ones to date for the direct synthesis of 1,2-dihydropyridines from imines and alkynes. Despite these notable advances, a more synthetically useful method should be broader in scope and enantioselective.[6,7] 1,2-Dihydropyridines are useful intermediates for the preparation of a wide range of valuable organic molecules.[8] Specifically, they have found applications in the synthesis of piperidines[9] and pyridines[10] and as Diels−Alder partners.[11] However, because of the lack of methods for the regio- and stereoselective formation of 1,2-dihydropyridines, their biological and synthetic potential remains largely unexplored. Herein we report a new and efficient asymmetric route to 1,2-dihydropyridines via rhodium-catalyzed [2+2+2] cycloaddition of diynes to sulfonimines.

We started with diyne **1a** bearing a *gem*-bis(methyl ester) tether and commercially available sulfonimine **2a**. Our study began with the identification of an effective catalytic system. Trials based on cobalt [CpCo(CO)$_2$, CpCo(C$_2$H$_4$)$_2$, CpCo(CO)(dmfu)[12]], nickel [Ni(cod)$_2$/PCy$_3$], ruthenium [Cp*Ru(cod)Cl], iridium ([Ir(cod)Cl]$_2$/dppe), and rhodium [RhCl(PPh$_3$)$_3$] catalysts[13] all failed to achieve the title reaction, as the starting materials were left untouched or cyclodimerization of the diyne took place. On the other hand, we found that catalytic combinations of [Rh(cod)$_2$]BF$_4$ with chelating diphosphines (10 mol% each) provided mixtures of the desired 1,2-dihydropyridine **3a** and cyclodimer **4** in 1,2-dichloroethane (DCE) at 80 °C (Table 1). The best compromise between

Table 1. Influence of Ligands and Reaction Conditions on the Rh-Catalyzed [2+2+2] Cycloaddition of Diyne 1a to Sulfonimine 2a



entry	ligand[a]	time (h)	conv (%)[b]	3a:4	yield of 3a (%)	ee of 3a (%)[c]
1	dppe	14	0	–	–	–
2	(*R*)-Binap	14	100	1:3	–	–
3	(*R*)-H$_8$-Binap	14	100	1:2.9	–	–
4	(*R*)-Segphos	14	50	1:1.4	–	–
5	(*R*)-DTBM-Segphos	14	0	–	–	–
6	(*R*)-Tol-Binap	14	100	1:1.7	–	–
7[d]	(*R*)-Tol-Binap	14	100	1:0	88	73
8[d,e]	(*R*)-Tol-Binap	14	100	1:0	60	66
9[d,e]	(*R*)-Tol-Binap	7	100	1:0	72	81

[a]See ref 13 for abbreviations. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by chiral HPLC. [d]With slow addition of **1a** using a syringe pump. [e]5 mol% [Rh(cod)$_2$]BF$_4$/(*R*)-Tol-Binap, 1.5 equiv of **2a**.

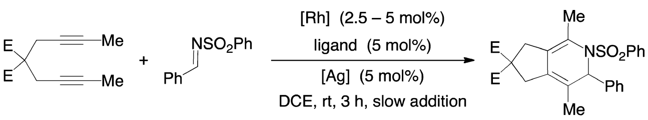
chemoselectivity and conversion was reached when (*R*)-Tol-Binap[13] was used (entry 6), yet even under these conditions, the diyne dimerization could not be annihilated. We anticipated that this issue could be circumvented by slow addition of diyne **1a** to a DCE solution of **2a** and Rh(I)$^+$/(*R*)-Tol-Binap (entries 7−9). As expected, the dimerization of diyne **1a** was suppressed, and dihydropyridine **3a** was isolated in satisfactory yields and enantioselectivities. Moreover, reducing the loading of the catalytic mixture to 5 mol%, the amount of imine to 1.5

Received: September 21, 2012
Published: March 4, 2013

equiv, and the addition time to 7 h afforded **3a** in a decent yield and, gratifyingly, with improved enantiomeric excess (entry 9).

We next looked for a milder catalytic process that would also afford better enantiocontrol (Table 2). Removal of the cod ligand by hydrogenation[14] allowed the catalyst to turn over at room temperature and the reaction time to be reduced to 3 h (entry 1). The product was still isolated in good yield (72%), but no improvement in the ee was observed (76%). The reaction could also be carried out with good efficiency in the presence of the neutral rhodium complex $[Rh(hexadiene)Cl]_2$ in association with a silver salt. Among the dimeric rhodium species and silver salts we screened, $[Rh(hexadiene)Cl]_2/AgSbF_6$ was the best combination at room temperature (3 h, 82%, 83% ee; entry 2). A subsequent survey of the biphosphane motif unveiled promising effects of more hindered ligands. We were pleased to find that the use of (*R*)-di*t*Bu-MeOBiphep[13] yielded **3a** in 77% yield with an excellent ee of 92% (entry 4). Control experiments revealed that the generation of a cationic rhodium species by the action of a silver salt was essential, with $AgSbF_6$ as the best candidate (entries 6 and 7).[15] Lastly, $[Rh(hexadiene)Cl]_2$ could not be replaced by the more common $[Rh(cod)Cl]_2$ (entry 8). Also, the use of a biphosphane ligand was critical for reaction efficiency, as the starting material remained unchanged without a biphosphane ligand under these specific conditions (entry 9).

Table 2. Optimization of the Reaction Conditions for Rh-Catalyzed [2+2+2] Cycloaddition of Diyne 1a to Sulfonimine 2a



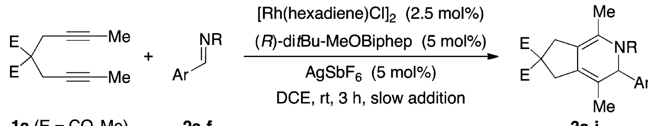
1a ($E = CO_2Me$) **2a** (1.5 equiv) **3a**

entry	[Rh]	ligand[a]	[Ag][b]	yield of 3a (%)	ee of 3a (%)[c]
1[d]	$[Rh(cod)_2]BF_4$	L_1	none	72	76
2[e]	$[Rh(hexadiene)Cl]_2$	L_1	$AgSbF_6$	82	83
3[e,f]	$[Rh(hexadiene)Cl]_2$	L_1	$AgSbF_6$	89	71
4[e]	$[Rh(hexadiene)Cl]_2$	L_2	$AgSbF_6$	77	92
5[e,f]	$[Rh(hexadiene)Cl]_2$	L_2	$AgSbF_6$	84	82
6[e]	$[Rh(hexadiene)Cl]_2$	L_2	$AgBF_4$	67	90
7[e]	$[Rh(hexadiene)Cl]_2$	L_2	none	0	0
8[g]	$[Rh(cod)Cl]_2$	L_2	$AgSbF_6$	0	0
9[e]	$[Rh(hexadiene)Cl]_2$	none	$AgSbF_6$	0	0

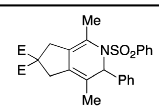
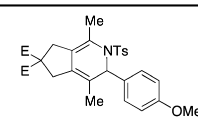
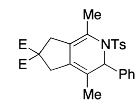
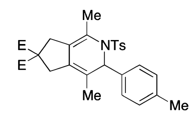
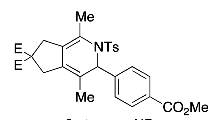
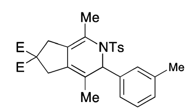
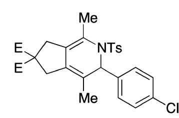
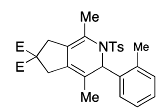
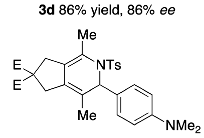
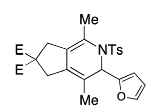
[a] L_1 = (*R*)-Tol-Binap; L_2 = (*R*)-3,5-di*t*Bu-MeOBiphep. [b] [Rh]/[Ag] = 1:1 when [Ag] was present. [c] Determined by chiral HPLC. [d] 5 mol% $[Rh(cod)_2]BF_4$ with previous hydrogenation. [e] 2.5 mol% $[Rh(hexadiene)Cl]_2$. [f] The reaction was carried out at 80 °C. [g] 2.5 mol% $[Rh(cod)Cl]_2$.

The scope of this asymmetric cycloaddition process was then assessed through variation of the diyne and sulfonimine components under the optimized conditions. We first examined the reactivity of various imines toward diyne **1a** (Table 3). Sulfonimines **2a** and **2b** (Ar = Ph) afforded the corresponding 1,2-dihydropyridines **3a** and **3b** in good yields with excellent enantiocontrol (entries 1 and 2). Unfortunately, sulfonimine **2c** bearing an electron-poor aryl group did not provide **3c** even at higher temperatures (entry 3). On the other hand, diyne **1a** was effectively converted into 1,2-dihydropyridines **3d–i** when reacted with sulfonimines bearing an electron-withdrawing group such as Cl (entry 4) or an electron-rich aryl group (entries 5–9). Ortho and meta substitution did not affect the enantioselectivity of the reaction (entries 8 and 9), but it was necessary to raise the temperature to 80 °C with these substrates. Finally, substitution of the imine with a heteroaromatic furan group gave dihydopyridine **3j**, albeit with moderate enantioselectivity (entry 10).

Table 3. Rhodium-Catalyzed [2+2+2] Cycloaddition: Imine Scope



1a ($E = CO_2Me$) **2a-f** (1.5 equiv) **3a-j**

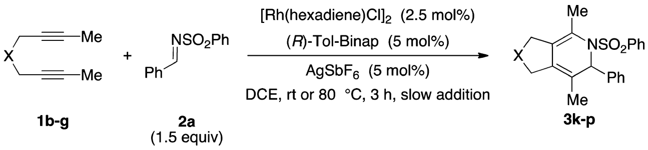
entry	product	entry	product
1	 **3a** 77% yield, 92% *ee*	6[b]	 **3f** 73% yield, 95% *ee*
2	 **3b** 77% yield, 96% *ee*	7[b]	 **3g** 83% yield, 93% *ee*
3[a]	 **3c** traces, ND	8[b]	 **3h** 56% yield, 95% *ee*
4[b]	 **3d** 86% yield, 86% *ee*	9[b]	 **3i** 60% yield, 94% *ee*
5[b]	 **3e** 65% yield, 94% *ee*	10[b,c]	 **3j** 54% yield, 61% *ee*

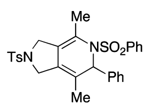
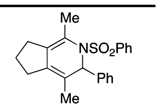
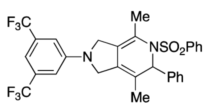
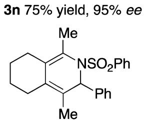
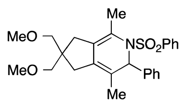
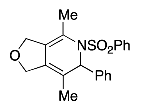
[a] No more conversion to the desired dihydropyridine **3c** could be observed at 80 °C. [b] The reaction was carried out at 80 °C. [c] The enantioselectivity could not be improved under various modified conditions.

We next focused on the diyne pattern, first varying the nature of the tether (Table 4). From the outset, we realized that the success of this reaction using diynes **1b–g** would require modified conditions. Knowing that slight variations in the tether or the phosphine ligand can have a dramatic influence on the reactivity of diyne systems,[16] we tested the less hindered (*R*)-Tol-Binap ligand. This time we observed satisfactory yields and enantioselectivities. Moreover, in some cases, higher temperatures favored initial conversion of the starting material and/or the desired cycloaddition process versus cyclodimerization. The nitrogen-tethered diyne **1b** (tosyl protecting group) remained unchanged at room temperature when reacted with sulfonimine **2a**, but at 80 °C, dihydropyridine **3k** was isolated in 99% yield at the expense of the enantioselectivity, which dropped to 4% ee (entry 1). Changing the tosyl group to an electron-poor benzene ring proved to be advantageous, giving product **3l** in good yield and ee at room temperature (entry 2).

dx.doi.org/10.1021/ja309301n | J. Am. Chem. Soc. 2013, 135, 4576–4579

Table 4. Rhodium-Catalyzed [2+2+2] Cycloaddition: Diyne Scope



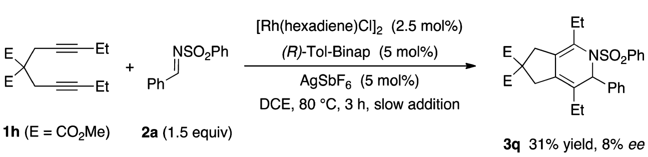
entry	product	entry	product
1[a]	 3k 99% yield, 4% *ee*	4[c]	 3n 75% yield, 95% *ee*
2[b]	 3l 81% yield, 81% *ee*	5[c]	 3o 82% yield, 96% *ee*
3[c]	 3m 76% yield, 91% *ee*	6[d]	 3p 68% yield, 92% *ee*

[a]The reaction was carried out at 80 °C, and subsequent ligand screening did not affect the enantioselectivity. [b]The reaction was carried out at room temperature. [c]The reaction was carried out at 80 °C. [d]The reaction was carried out at room temperature with 3 equiv of **2a**.

Diynes displaying a carbon tether could be used as well, giving rise to 1,2-dihydropyridines **3m**–**o** at 80 °C in good yields with ee's of >90% (entries 3–5). Finally, the oxygen-tethered diyne **1g** proved to be more reactive, with the cyclization taking place at room temperature with very good enantiocontrol (entry 6).

Changing the methyl group at the alkyne termini had a dramatic influence on the reactivity. While tolerated, substitution with ethyl groups gave a moderate yield of the corresponding 1,2-dihydropyridine **3q** with low enantioselectivity (31% yield, 8% ee; Scheme 1).

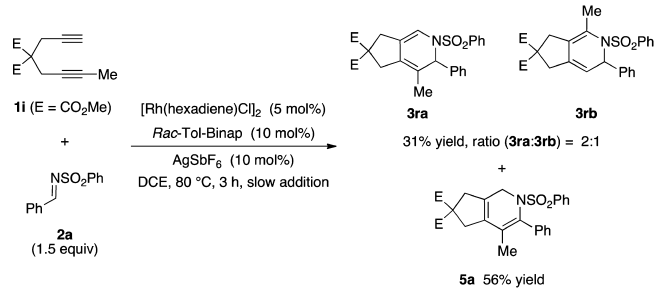
Scheme 1. Rh-Catalyzed [2+2+2] Cycloaddition of Diyne 1h to Sulfonimine 2a



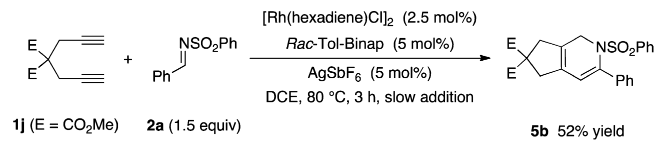
At 80 °C, the unsymmetrical diyne **1i** was transformed into a mixture of three products that could be partially separated (Scheme 2). Two were the expected dihydropyridines **3ra** and **3rb**, which were obtained with low regioselectivity (2:1, 31% yield). The major product was the regioisomeric dihydropyridine **5a** (56% yield). Additional experiments showed that **5a** did not arise from **3ra**.[17] Finally, fully nonsubstituted diyne **1j** afforded **5b** exclusively (Scheme 3).

To explain the formation of the various products depicted above, the following mechanism is proposed (Scheme 4). Typically, initial coordination of diyne **1** followed by oxidative cyclization (OC) would generate rhodacyclopentadiene **A**. Next, regioselective insertion of sulfonimine **2** would afford rhodadihydroazepine **B** stabilized by the coordination of the

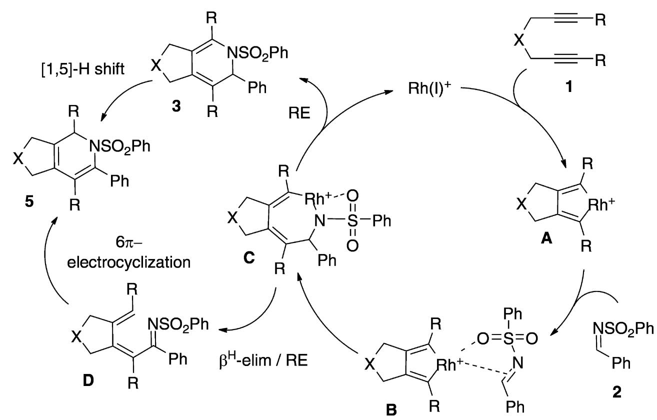
Scheme 2. Attempted Rh-Catalyzed [2+2+2] Cycloaddition of Unsymmetrical Diyne 1i to Sulfonimine 2a



Scheme 3. Attempted Rh-Catalyzed [2+2+2] Cycloaddition of Nonsubstituted Diyne 1j to Sulfonimine 2a



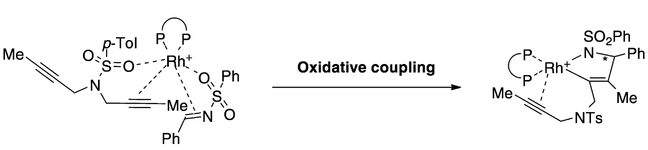
Scheme 4. Proposed Mechanism for the Rhodium-Catalyzed Cycloaddition of Diynes and Sulfonimines



sulfonyl group to rhodium. Subsequent reductive elimination (RE) would furnish the desired 1,2-dihydropyridine **3**. In the case of unsymmetrical or nonsubstituted diynes, a β^H-elimination/RE sequence may occur, leading to the nonisolated intermediate **D**.[18] A 6π electrocyclization of **D** would furnish the more stable dihydropyridine **5**, which could also arise from dihydropyridine **3** by a classic [1,5]-H shift. In contrast with Ogoshi's and Yoshikai's works under nickel catalysis,[4,5] initial formation of the corresponding rhodapyrroline after OC of one alkyne moiety and the imine was not considered because of the tendency of the diyne to cyclodimerize under these catalytic conditions.

The low enantiocontrol observed with the tosylamide-linked 1,6-diyne **1b** suggests that an alternative pathway is possible in this case. The sulfonamide group would allow the formation of a rhodapyrroline intermediate.[14,19] Thus, the asymmetric induction would be low because of the distance between the ligand and the newly formed stereogenic center (Scheme 5). Also, formation of a rhodacyclopentadiene with diyne **1h** would be sluggish because of steric hindrance due to the ethyl groups (Scheme 1), so the former rhodapyrroline intermediate would be involved, justifying the low enantioselectivity observed in that case.

Scheme 5. Mechanistic Proposal for Tosylamide-Linked Diyne 1b



In conclusion, the first asymmetric transition-metal-catalyzed [2+2+2] cycloaddition of diynes to sulfonimines is reported, providing a new, efficient method for the synthesis of enantioenriched 1,2-dihydropyridines. These heterocycles can be readily accessed through a Rh-catalyzed cyclization under mild conditions. Further investigations regarding this enantioselective reaction are underway, including its extension to the challenging case of unsymmetrical diynes and computational studies to elucidate the mechanistic details and the origin of the selectivity.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data and experimental details for cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by Université Pierre et Marie Curie-Paris 6, CNRS, IUF, and Servier Corporation.

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