Use of achiral additives to increase the stereoselectivity in Rh(II)-catalyzed cyclopropanations†‡

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We describe our studies on the effect of various Lewis bases and Brønsted acids as achiral additives on the stereoselectivity of some Rh(II)-catalyzed cyclopropanations.

Over the past two decades, stereoselective Rh(II)-catalyzed cyclopropanation reactions have received much attention.[1] These methods have been demonstrated to be among the most reliable means of accessing chiral 1,1-disubstituted cyclopropanes. Donor–acceptor Rh(II)-carbenes are well established to provide high levels of diastereocontrol.[1a] As such, many reports of highly enantio- and diastereoselective cyclopropanations using diazo reagents bearing an acceptor and a donor group have been described.[2] However, little is known about the stereoselective cyclopropanation using diazo reagents bearing two acceptor groups.[3] Indeed, low levels of enantio- and diastereocontrol are associated with such reagents. As part of our research program aimed at addressing these issues, we recently reported several highly enantio- and diastereoselective reactions using diazo reagents bearing two acceptor groups.[4–6] During the course of these studies, we observed the important effect of various achiral additives on the corresponding selectivity. The purpose of this communication is to describe our results on the study of the effect of achiral Lewis bases and Brønsted acids as additives on stereoselective Rh(II)-catalyzed cyclopropanation reactions.[7,8]

During our work towards developing a highly stereoselective method for the synthesis of cyclopropane **3a**, we observed that diazo **1a** was quite stable to Rh(II)-catalyzed decomposition (Fig. 1). In some reactions that did not go to completion, the residual diazo starting material was recovered. To fully consume the unreacted diazo **1a** and to facilitate purification of the corresponding cyclopropane **3a**, we considered adding different Brønsted acids to decompose this residual diazo compound. Surprisingly, **1a** was found to be quite stable to acidic media as well, but performing the reactions in the presence of these acidic additives, in catalytic amounts, affected the enantioselectivity (Table 1).[4b] Indeed, sulfonic amide additives displayed a non-negligible effect (entries 8–10). $TfNH_2$ was found to be optimal, increasing the enantioselectivity from 49 : 1 er to 57 : 1 er (entry 8). Interestingly, none of the Lewis bases examined led to an increase of the selectivity (entries 2–6). Instead, the catalyst was deactivated by these bases, leading to a low consumption of diazo **1a**, consequently affording a low yield of the desired cyclopropane **3a**. In all cases (Table 1), the investigated additives had no effect on the diastereoselectivity of this reaction.

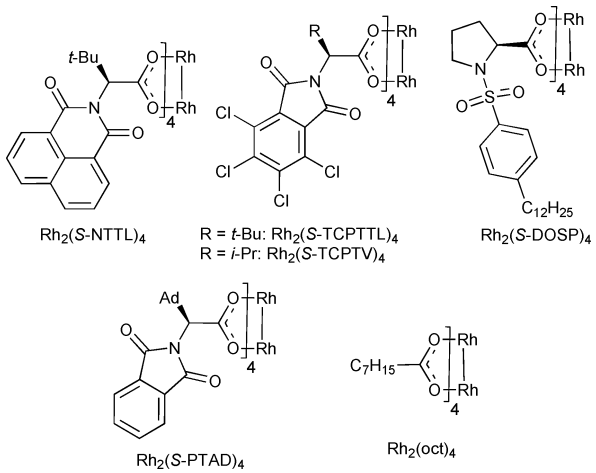
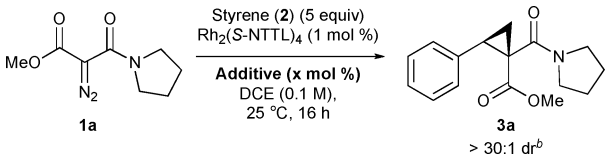


Fig. 1 Structures of different Rh(II) catalysts.

Table 1 Study of the effect of achiral additives on the stereoselective formation of **3a**



Entry	Additive (*x*)	Yield (%)[a]	er[c]
1	None	79	49 : 1
2	DMAP (10)	—	—
3	DMAP (1)	10	ND
4	Pyridine (1)	14	ND
5	MeCN (10)	67	49 : 1
6	DMF (10)	62	49 : 1
7	AcOH (10)	73	49 : 1
8	$TfNH_2$ (10)	78	57 : 1
9	$MsNH_2$ (10)	75	39 : 1
10	$TsNH_2$ (10)	75	28 : 1

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture using an internal standard. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by SFC analysis on a chiral stationary phase.

Interested by the stereoselective formation of cyclopropane **3b**, we developed conditions to obtain **3b** in 10 : 1 dr and 13 : 1 er (Table 2, entry 1). Cognizant of the effect of different additives on the formation of **3a**, we considered their application in the synthesis of **3b**.[4af] Performing the reaction with 10 mol% of different Lewis bases led to a negative effect on the selectivity (entries 2–6).

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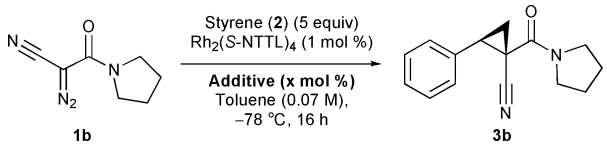
‡ Electronic supplementary information (ESI) available: General experimental procedures. See DOI: 10.1039/b920587j

Table 2 Study of the effect of achiral additives on the stereoselective formation of **3b**



Entry	Additive (*x*)	Yield (%)[a]	dr[b]	er[c]
1	None	73	10 : 1	13 : 1
2	DMAP (10)	14	6 : 1	9 : 1
3	DMAP (1)	62	7 : 1	10 : 1
4	Pyr (1)	59	8 : 1	6 : 1
5	MeCN (10)	81	10 : 1	12 : 1
6	DMF (10)	78	10 : 1	7 : 1
7	AcOH (10)	77	12 : 1	10 : 1
8	$TfNH_2$ (10)	77	24 : 1	39 : 1
9	$MsNH_2$ (10)	80	16 : 1	24 : 1
10	$TsNH_2$ (10)	75	9 : 1	5 : 1
11	TfOH (10)	—	—	—
12	Tf_2NH (10)	67	2 : 1	2 : 1

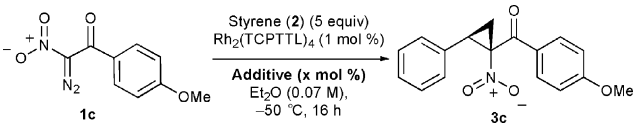
[a] Determined by ^{1}H NMR spectroscopy of the crude mixture using an internal standard. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by SFC analysis on a chiral stationary phase.

However, Brønsted acids improved the selectivity of the reaction quite remarkably (entries 7–12). We were pleased to isolate the desired cyclopropane **3b** in 24 : 1 dr and 39 : 1 er when 10 mol% of $TfNH_2$ was used in the reaction (entry 8). This represents a significant increase relative to the selectivity of 10 : 1 dr and 13 : 1 er obtained without the use of additive (entry 1). Other sulfonamides also affected the selectivity but $TfNH_2$ was found to be optimal (entries 8–10). More acidic Tf_2NH led to decreased levels of selectivity while TfOH led to a complex mixture of products (entries 11–12). This is presumably due to the low stability of diazo **1b** in the presence of highly acidic compounds.

Based on these results, we were intrigued by the effect of additives in other Rh(II)-catalyzed cyclopropanations. We recently reported a highly enantio- and diastereoselective formation of 1-nitro-1-phenylketone cyclopropane **3c** using Rh_2(*S*-TCPTTL)$_4$.[4d] We studied the use of a variety of Lewis bases and Brønsted acids in this reaction (Table 3). None of the Brønsted acids investigated increased the selectivity. To our delight, we found that the use of 1 mol% of DMAP improved the enantioselectivity from 27 : 1 er to 39 : 1 er (entry 3). Increasing the amount of DMAP led to decreased yields with no further improvement in selectivity (entry 2). The DMAP effect was only observed at low temperature as the selectivity was not affected when the reaction was performed at 0 °C (entries 8–9). A possible explanation is that the uncomplexed and more reactive Rh_2(*S*-TCPTTL)$_4$ is present at room temperature giving access to a faster Rh_2(*S*-TCPTTL)$_4$-catalyzed process (Fig. 2). However, at low temperature, Rh_2(*S*-TCPTTL)$_4$·DMAP is formed exclusively. The Rh_2(*S*-TCPTTL)$_4$·DMAP is a less active catalyst that would favour a later transition state, enhancing the enantioinduction according to the Hammond postulate.

We next investigated the effect of these additives on the diastereoselective Rh_2(oct)$_4$-catalyzed reaction involving diazo **1d** (Table 4).[5b] Interestingly, none of the additives investigated above significantly increased the diastereoselectivity, suggesting

Table 3 Study of the effect of achiral additives on the stereoselective formation of **3c**



Entry	Additive (*x*)	Yield (%)[a]	dr[b]	er[c]
1	None	80	49 : 1	27 : 1
2[d]	DMAP (5)	42	32 : 1	39 : 1
3	DMAP (1)	78	32 : 1	39 : 1
4	Pyr (1)	70	32 : 1	32 : 1
5	AcOH (10)	77	49 : 1	28 : 1
6	$TfNH_2$ (10)	85	49 : 1	28 : 1
7	$MsNH_2$ (10)	89	49 : 1	28 : 1
8[e]	None	68	16 : 1	14 : 1
9[e]	DMAP (1)	70	16 : 1	14 : 1

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by SFC analysis on a chiral stationary phase. [d] Reaction time of 48 h. [e] Reaction performed at 0 °C.

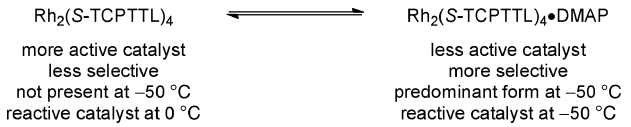
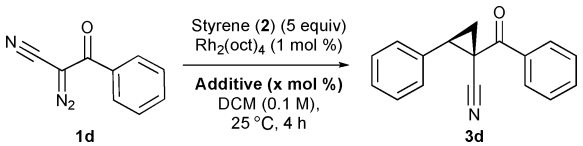


Fig. 2 Reactive catalyst.

Table 4 Study of the effect of achiral additives on the stereoselective formation of **3d**



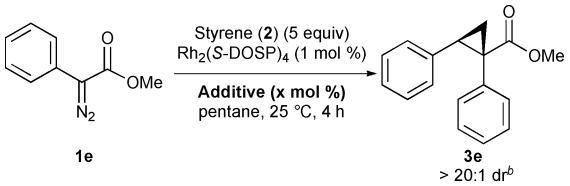
Entry	Additive (*x*)	Yield (%)[a]	dr[b]
1	None	97	7 : 1
2	DMAP (10)	17	7 : 1
3	Pyridine (10)	74	8 : 1
4	DMF (10)	91	7 : 1
5	MeCN (10)	93	7 : 1
6	AcOH (10)	96	7 : 1
7	$TfNH_2$ (10)	96	7 : 1
8	$MsNH_2$ (10)	97	7 : 1

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture using an internal standard. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture.

that the additives in the previous reactions might display their effects on the chiral environment induced by the chiral catalyst.

When we studied the formation of **3d**, we observed that diazo reagent **1d** and the *in situ* generated iodonium ylide reagent derived from **4** afforded different level of diastereoselectivity in their respective Rh_2(oct)$_4$-catalyzed reactions (eqn (1)–(2)).[5b] However, performing the same reaction with diazo **1d** in the presence of $PhI(OAc)_2$ and Na_2CO_3 as additives furnished a 86 : 14 dr for the desired compound, that is the same diastereoselectivity observed with the reaction involving **4**. This negative effect of achiral additives in a Rh_2(oct)$_4$-catalyzed cyclopropanation reaction suggests that

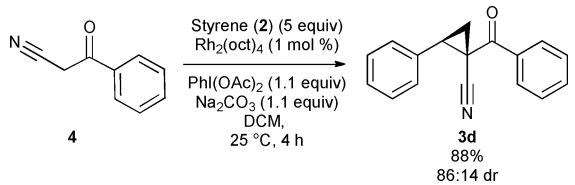
Table 5 Study of the effect of achiral additives on the stereoselective formation of **3e**



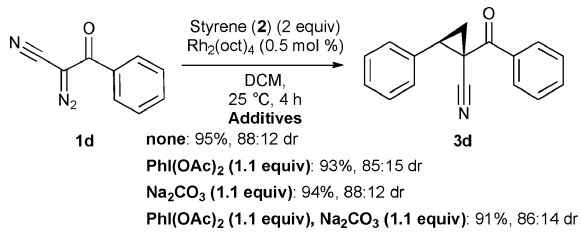
Entry	Additive (x)	Yield (%)[a]	er[c]
1	None	85	16 : 1
2	DMAP (10)	24	14 : 1
3	DMAP (1)	72	16 : 1
4	AcOH (10)	84	16 : 1
5	MeCN (10)	83	14 : 1
6	DMF (10)	86	13 : 1
7	$TfNH_2$ (10)	88	8 : 1
8	$TfNH_2$ (50)	80	8 : 1
9	$MsNH_2$ (10)	77	10 : 1

[a] Determined by ^{1}H NMR spectroscopy of the crude mixture using an internal standard. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by SFC analysis on a chiral stationary phase.

both processes might go through the same Rh-carbene intermediate.



(1)



(2)

Finally, we investigated the effect of these additives on the stereoselective cyclopropanation using donor–acceptor diazo reagent **1e** and Rh_2(*S*-DOSP)$_4$ as catalyst (Table 5).[9] Unfortunately, $TfNH_2$ and $MsNH_2$ led to decreased levels of selectivity, presumably due to the low stability of these diazo reagents toward these acids (entries 7–9). Though weaker acids do not decompose these reagents, virtually no effect was observed on the selectivity (entry 4). Unfortunately, none of the Lewis bases investigated afforded the desired cyclopropane with enhanced results (entries 2, 3, 5, 6). Though these additives are not suitable in the reaction, Davies and Venkataramani have reported that methylbenzoate can increase the selectivity of this reaction at low catalyst loading.[7a] This demonstrates the differences in electronics between diacceptor and donor–acceptor carbenes.

In conclusion, we have demonstrated that various achiral additives such as Lewis bases and Brønsted acids can sometimes display moderate to important effects on the stereoselectivity of different Rh(II)-catalyzed cyclopropanations. $TfNH_2$ and DMAP have been shown to be optimal with Rh_2(*S*-NTTL)$_4$ and Rh_2(*S*-TCPTTL)$_4$, respectively, suggesting a correlation between the additive and the corresponding symmetry of the catalyst with a carbene possessing two acceptors groups. Unfortunately, donor–acceptor Rh(II)-carbenes have not been positively influenced by the additives investigated in the current study. Work taking advantage of these effects of additives is under investigation and will be reported in due course.

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