J|A|C|S COMMUNICATIONS

Published on Web 04/30/2009

$TfNH_2$ as Achiral Hydrogen-Bond Donor Additive to Enhance the Selectivity of a Transition Metal Catalyzed Reaction. Highly Enantio- and Diastereoselective Rhodium-Catalyzed Cyclopropanation of Alkenes Using α-Cyano Diazoacetamide

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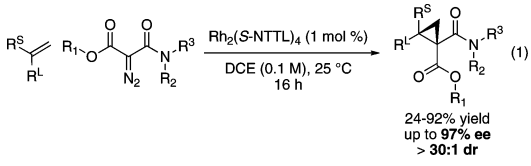
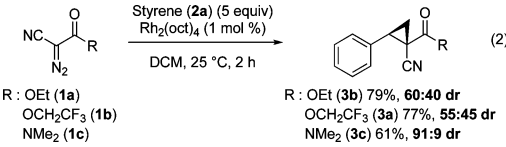
Methods applied toward the synthesis of chiral, nonracemic molecules have undergone dramatic transformations over the past decades. A large number of stoichiometric processes involving chiral reagents have been gradually replaced by catalytic reactions. More recently, chiral organocatalysts have been developed to complement transition metal catalyzed processes.[1] Chiral alcohols,[2] phosphoric acids,[3] and thioureas[4] have been utilized as hydrogen-bond donors in the synthesis of various enantioenriched molecules. The purpose of this communication is to document the unprecedented positive influence of an *achiral* hydrogen-bond donor additive, used in catalytic amounts, on both the enantio- and diastereoselectivities of a metal catalyzed reaction.

Chiral nitrile-substituted cyclopropanes are of great interest as they are versatile templates for the rapid formation of biologically active and synthetically useful functionalized cyclopropane derivatives.[5,6] In recent years, the use of transition metal catalyzed decomposition of diazo reagents has proven to be a general method in intermolecular cyclopropanation.[7] Although many catalysts have demonstrated high efficiency with diazoacetate reagents,[7] few studies reported the effective use of diazoacetonitrile derivatives in asymmetric cyclopropanation.[8−10] Recently, Davies described the use of α-phenyl diazoacetonitrile in an asymmetric Rh(II)-catalyzed cyclopropanation of olefins.[11] Although excellent diastereomeric ratios (dr) were obtained (95:5−97:3), which is typical for donor−acceptor carbenes, the enantiomeric excesses (ee) were moderate to good (78−90% ee) and the reaction was limited to aryl-substituted olefins. As part of our general interest to develop the enantio- and diastereoselective transition metal catalyzed cyclopropanation of olefins using diazo reagents bearing two acceptor groups, we recently introduced amides as powerful *trans*-directing groups.[12] For example, very high levels of enantio- and diastereoselection were obtained using α-amido diazoacetate reagents (eq 1).



(1)

Unfortunately, this reaction suffered from many limitations. *o*-Substituted styrenes and electron-poor styrenes afforded the corresponding cyclopropanes in low yields while alkyl substituted olefins were unreactive. To address these serious limitations of both the latter methodology and the formation of nitrile-containing cyclopropanes, we focused our efforts toward the asymmetric construction of substituted 1-cyanocyclopropane-1-carboxy derivatives.



(2)

Initially, the reaction was attempted using ethyl α-cyanodiazoacetate (**1a**) (eq 2). Poor diastereoselectivity was observed with styrene, highlighting the diastereocontrol issue associated with metal carbenes bearing two different acceptor groups. As expected, the less polar trifluoroethylesters **1b** reacted with reduced diastereocontrol even though ester **1b** is slightly more sterically demanding than ester **1a**. However, by benefiting from the greater *trans*-directing ability of an amide,[12] a substantial increase of the diastereoselectivity (from 60:40 to 91:9) was obtained when diazo **1c** was employed.

To achieve a highly enantioselective process, chiral ligands were screened using amide derivatives **1c**−**e** (Figure 1). With diazo reagents **1c** and **1d**, Hashimoto's $Rh_2(S\text{-TCPTV})_4$[13] was optimal giving the corresponding cyclopropane with moderate ee (entry 1−2, Table 1 and Table S1−3).[14] Interestingly, when using diazo **1e**, low enantiocontrol was observed with $Rh_2(S\text{-TCPTV})_4$ (entry 3), but $Rh_2(S\text{-NTTL})_4$[15] showed a promising level of selectivity (entry 4). The use of aromatic solvents (entries 5−6) and lower temperatures increased both the dr and ee (entry 7). A concentration of 0.07 M in toluene at −78 °C afforded the cyclopropane **3e** with 91:9 dr and 86% ee (entry 8).

During our work aimed at describing the *trans*-directing ability of the amide group (eq 1),[12] we observed that in some cases the diazo was not fully consumed during the reaction. To facilitate the purification, we envisioned decomposing the residual diazo reagent via the addition of a Brønsted acid. Unfortunately, we found that diazo reagents bearing two acceptors groups were quite stable to an acidic medium. However, we found that conducting the reaction in the presence of a Brønsted acid afforded increased enantioselectivity (*vide infra*). Though diazo **1c**−**e** were fully consumed in all reactions performed in the current study, we envisioned looking for the effect of various Brønsted acids as additives (10 mol %) on the selectivity (Table 2). Unfortunately carboxylic acids, phosphoric acid, phenol, aniline, or benzamide did not affect the selectivity positively. It should be pointed out that the X−H insertion product is not observed by analysis of the crude ^1H NMR. Gratifyingly, higher selectivities were observed when different sulfonamides were added. *Indeed, the selectivity of 86% ee and 91:9 dr observed without the additive improved spectacularly to 95% ee and 96:4 dr by conducting the reaction in the presence of 10 mol % of* $TfNH_2$. Several other sulfonamides were tested, but $TfNH_2$ was found to be superior.

10.1021/ja902205f CCC: $40.75

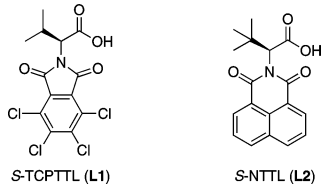
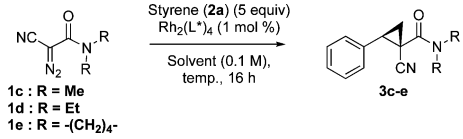


Figure 1. Ligands L*H for $Rh_2(L^*)_4$-catalyzed cyclopropanations.

Table 1. Optimization of the Asymmetric Cyclopropanation Involving α-Cyano Diazoacetamides



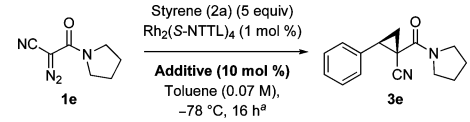
entry	L*	solvent	temp (°C)	yield[a] (%)	dr[b] *t*:*c*	% ee[c] (*t*)
1[d]	L1	ether	−40	69	97:3	59
2[e]	L1	ether	25	49	91:9	30
3[f]	L1	ether	25	51	88:12	3
4[f]	L2	DCM	25	67	83:17	63
5[f]	L2	PhMe	25	58	85:15	70
6[f]	L2	PhH	25	65	85:15	73
7[f]	L2	PhMe	−78	74	91:9	84
8[f,g]	L2	PhMe	−78	73	91:9	86

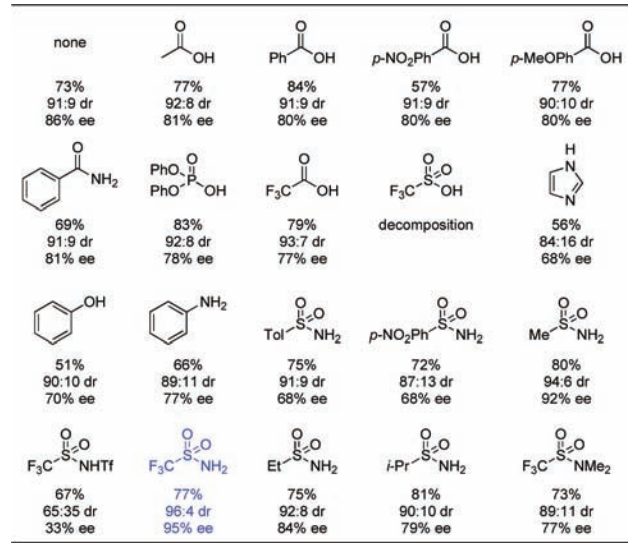
[a] ^{1}H NMR yield of the *trans*-isomer determined using trimethoxybenzene as internal standard. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by SFC on chiral stationary phase. [d] Diazo **1b** was used. [e] Diazo **1c** was used. [f] Diazo **1d** was used. [g] Performed at 0.07 M.

To the best of our knowledge, this represents the first example of the positive influence of an achiral hydrogen-bond donor additive on both the enantio- and the diastereoselectivities in a metal catalyzed reaction.[16] Increasing the amount of $TfNH_2$ did not increase the selectivity while using less than 10 mol % was found to be detrimental on the selectivity. To facilitate the reaction setup, we found that a mixture of **1e**/$TfNH_2$ (10 mol %) can be stored at 0 °C and used directly in the reaction. Although an increase in catalyst loading improved the yield (Table 3, entries 1−3), 1 mol % was chosen for the remainder of the study due to cost considerations. Furthermore, although the diazo reagent can be added to the reaction mixture at −78 °C in one portion, a slight increase in yields (5−10%) was noted when it was added over a 2-h period.

Under these optimal conditions, we were pleased to observe that a large variety of mono- and disubstituted olefins underwent the reaction in good yields with excellent dr and ee (Table 3). Monosubstituted styrenes containing electron-donating and -withdrawing substituents are converted to the corresponding cyclopropanes in high yields and stereoselectivities (entries 1−20). Monosubstituted electron-rich olefins gave the desired products with slightly lower selectivity, but with higher yields than electron-poor olefins (entries 16−18 vs entries 17, 19−20). Unlike other methodologies,[12] steric hindrance was not detrimental. Similar yields, dr, and ee were obtained with a variety of *o*-substituted styrenes (entries 10−15, 20). More importantly, alkyl-substituted olefins that are often unreactive in Rh-catalyzed cyclopropanations[7] successfully afforded the corresponding cyclopropanes with moderate yields and excellent selectivity (entries 25−29). 1,1-Disubstituted olefins such as α-methyl styrene and *Z*-disubstituted alkenes such as indene also led to their corresponding cyclopropanes in good yields as well as excellent selectivity (entries 21−24). In some

Table 2. Effect of Different Additives on the Asymmetric Cyclopropanation Using Diazo **1e**

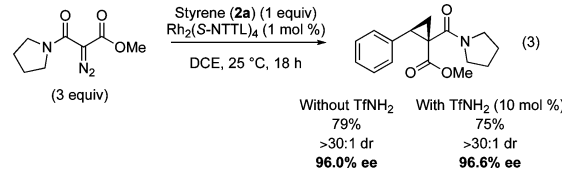




[a] ^{1}H NMR yield of the *trans*-isomer determined using trimethoxybenzene as internal standard. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture. Enantiomeric excesses were determined by SFC on chiral stationary phase.

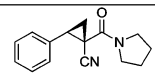
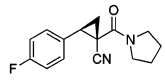
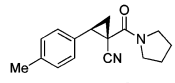
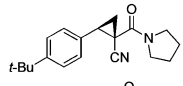
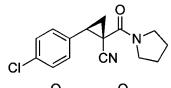
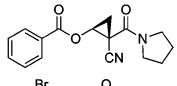
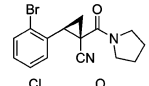
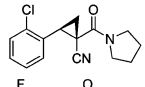
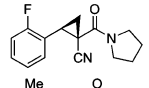
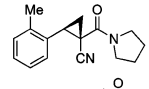
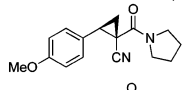
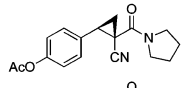
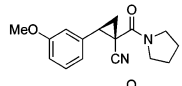
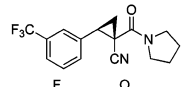
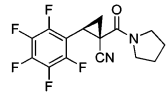
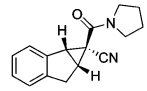
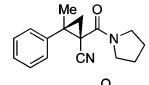
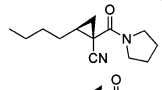
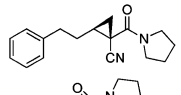
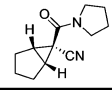
cases, we demonstrated that increasing the catalyst loading could lead to improved dr, ee, and yields (entries 9, 11, 15, 22, 23).

The exact mode of action of $TfNH_2$ in increasing the ee and dr remains unclear. We determined by ^{1}H NMR and LCMS analysis that $TfNH_2$ does not undergo ligand exchange or complexation with Rh_2(*S*-NTTL)$_4$.[17] $TfNH_2$ might also prevent the catalyst from decomposition.[16a] Conversely, ^{13}C NMR analysis of a $TfNH_2$/**1e** mixture demonstrated different chemical shifts for both the amide and nitrile carbon compared to **1e** alone. $TfNH_2$ might interact with one of these functional groups while being on the metal carbene affecting the position of the chiral ligands on the Rh. This would also increase the reactivity of the metal carbene explaining why only a catalytic amount of the additive can be used. We believe that it interacts preferentially with the cyano group, as performing the reaction with an α-amido diazoacetate reagent[12] and $TfNH_2$ (10 mol %) only led to an increase of 0.6% ee, presumably due to the lower basicity of the ester group (eq 3). Furthermore, conducting the reaction (Table 1, entry 8) in the presence of MeCN (100 mol %) and $TfNH_2$ (10 mol %) led to lower selectivity (95:5 dr, 92% ee) compared to $TfNH_2$ alone (96:4 dr, 95% ee), while MeCN (100 mol %) alone had no negative effect (91:9 dr, 85% ee), also suggesting that $TfNH_2$ interacts with the cyano moiety.



In summary, we have described a highly enantio- and diastereoselective synthesis of 1-cyanocyclopropanes-1-carboxy derivatives. A variety of mono- and disubstituted olefins afforded the

Table 3. Scope of the Cyclopropanation[a]

entry	product	yield (%)[b]	dr *t*:*c*[c]	% ee (*t*)[d]
1	 (**3e**)	74	96:4	**95**
2[e]		80	97:3	**96**
3[g]		87	97:3	**97**
4	 (**3f**)	73	97:3	**95**
5	 (**3g**)	77	97:3	**95**
6	 (**3h**)	70	96:4	**96**
7	 (**3i**)	75	98:2	**96**
8	 (**3j**)	68	97:3	**86**
9[e]		79	98:2	**89**
10[f]	 (**3k**)	64	98:2	**91**
11[e]		71	98:2	**91**
12	 (**3l**)	62	97:3	**94**
13	 (**3m**)	70	98:2	**96**
14	 (**3n**)	53	95:5	**94**
15[e]		61	96:4	**94**
16	 (**3o**)	85	91:9	**92**
17	 (**3p**)	84	93:7	**94**
18	 (**3q**)	81	95:5	**92**
19	 (**3r**)	65	97:3	**94**
20	 (**3s**)	68	98:2	**98**
21	 (**3t**)	71	99:1	**87**
22[e]		78	99:1	**89**
23[g]		79	99:1	**89**
24	 (**3u**)	63	85:15	**91**
25	 (**3v**)	68	93:7	**≥90**[h]
26[i]		73	93:7	**≥90**[h]
27	 (**3w**)	65	93:7	**92**
28	 (**3x**)	62	99:1	--[j]
29[i]		70	99:1	--[j]

[a] Diazo **1d** (1 equiv), alkene (5 equiv), $TfNH_2$ (10 mol %), Rh_2(*S*-NTTL)$_4$ (1 mol %), toluene, 0.07 M, −78 to 25 °C, 16 h. [b] Isolated yields of the major *trans*-isomer. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by SFC on chiral stationary phase. [e] Using 2 mol % of catalyst. [f] (1*S*,2*R*)-Absolute stereochemistry determined by X-ray analysis. [g] Using 5 mol % of catalyst. [h] Determined on a derivative. [i] 10 equiv of alkene were used. [j] Product is meso.

corresponding cyclopropane in moderate to good yields and excellent selectivity. Finally, this work featured the unprecedented use of an achiral hydrogen-bond donor as an additive to enhance the selectivity and exploited the powerful *trans*-directing ability of the amide group in Rh(II)-catalyzed cyclopropanations. Further work to establish the exact role of the $TfNH_2$ is in progress and will be reported in due course.

Acknowledgment. This work was supported by NSERC (Canada), the Canada Research Chair Program, and the Université de Montréal. D.M. is grateful to NSERC (PGS D), the Université de Montréal, and the Financière Manuvie for postgraduate fellowships. S.A. is grateful to NSERC (USRA) for undergraduate fellowship. Francine Bélanger, and Jad Tannous (Université de Montréal) are acknowledged for X-ray and SFC analysis, respectively.

Supporting Information Available: Experimental procedures for the preparation of all the compounds and characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA902205F