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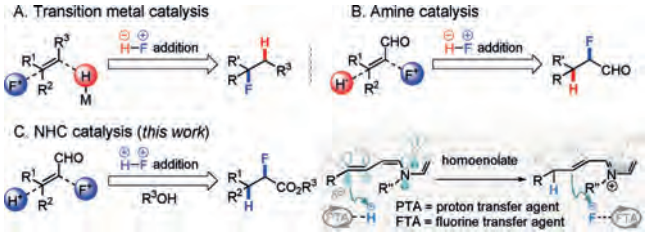
Enantio- and Diastereoselective Hydrofluorination of Enals by N-Heterocyclic Carbene Catalysis

Leming Wang, Xinhang Jiang, Jiean Chen, and Yong Huang**

Abstract: *In contrast to well-established asymmetric hydrogenation reactions, enantioselective protonation is an orthogonal approach for creating highly valuable methine chiral centers under redox-neutral conditions. Reported here is the highly enantio- and diastereoselective hydrofluorination of enals by an asymmetric β-protonation/α-fluorination cascade catalyzed by N-heterocyclic carbenes (NHCs). The two nucleophilic sites of a homoenolate intermediate, generated from enals and an NHC, are sequentially protonated and fluorinated. The results show that controlling the relative rates of protonation, fluorination, and esterification is crucial for this transformation, and can be accomplished using a dual shuttling strategy. Structurally diverse carboxylic acid derivatives with two contiguous chiral centers are prepared in a single step with excellent d.r. and ee values.*

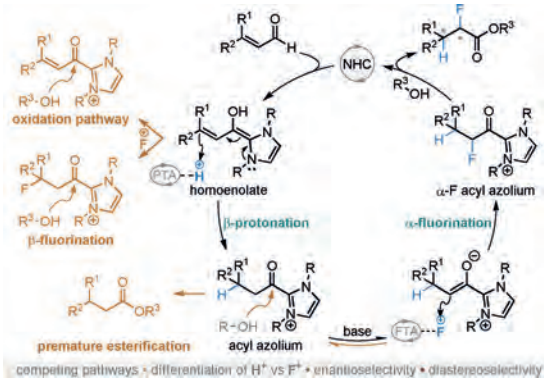
There is much interest in the development of general synthetic strategies towards fluorine-containing compounds because of their broad applications of in pharmaceuticals and agrochemicals.[1] Direct, asymmetric hydrofluorination is particularly attractive given the abundance of common olefinic chemical feedstocks.[2] However, introduction of two contiguous chiral centers, one of which bears a fluorine, in a single process is very challenging. Asymmetric metal hydride addition to olefins followed by trapping of the corresponding organometallic species with a fluorine source has been reported (Scheme 1 A).[3] MacMillan et al. reported a formal asymmetric addition of H^-F^+ to electron-deficient olefins using iminium/enamine catalysis (Scheme 1 B).[4] These approaches use reducing reagents for the hydride transfer and oxidative conditions for the fluorination, and proceeds in either a sequential or stepwise manner. Herein, we report a complementary strategy of formal asymmetric addition of H^+F^+ to enals by an enantioselective β-protonation/diastereoselective α-fluorination/esterification cascade (Scheme 1 C). This redox neutral transformation demonstrates wide functional-group tolerance across various structural motifs.

Recently, asymmetric protonation reactions catalyzed by N-heterocyclic carbenes (NHC) emerged as a general, redox-neutral strategy for the synthesis of β-chiral carboxy derivatives. In 2015, Scheidt et al. reported asymmetric hydrogenation of β-ester enals, a reaction which was later extended to β,β-aryl, alkyl enals by the same group.[5] In 2017, our group reported enantioselective hydrogenation of enals using bridgehead nitrogen amines as a selective proton-transfer agent.[6] Subsequently, we discovered that the same transformation can be accomplished with a broader substrate scope by using a combination of an achiral NHC and a chiral phosphoric acid.[7] We recently applied this strategy to the synthesis of β-chiral amides, hydrazides, acid, esters, peresters, and heterocycles.[8] However, all asymmetric β-protonation reactions mentioned above are only applicable to products lacking an α-chiral center. We envisioned that upon β-protonation of the homoenolate intermediate, the resulting acyl azolium species could be intercepted by an electrophilic fluorinating agent under basic conditions to give the formal hydrofluorination product with contiguous α- and β-chiral centers (Scheme 2).



Scheme 1. Asymmetric hydrofluorination of olefins.

Sun and Wang reported enantioselective α-fluorination of acyl azolium compounds using aliphatic aldehydes.[9] However, their protocols cannot be extended to β-protonation because of the absence of a proton source in the reaction. Mechanistically, combining β-protonation and α-fluorination



Scheme 2. Plausible reaction pathways of asymmetric hydrofluorination by NHC-mediated homoenolate intermediates.

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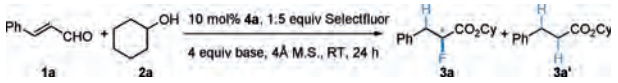
presents several challenges, with the first being chemoselectivity. In the proposed catalytic cycle (Scheme 2), there are two reactive electrophiles, H^+ and F^+, and the β-carbon center of the homoenolate needs a way to differentiate between them. The second challenge is premature esterification of the acyl azolium intermediate prior to α-fluorination. It has been demonstrated that esterification is facile using alcohols as NHC turnover agents[10] and consequently, to accomplish effective α-fluorination, slowing down esterification and increasing basicity of the reaction media are necessary. However, once α-fluorination is accelerated by increasing the concentration of the enolate, the β-protonation will inevitably be compromised because of the low concentration of protons. As a result, complications might arise from β-fluorination or direct oxidation of the homoenolate. We recently found that oxidation of homoenolates to α,β-unsaturated esters predominates when the concentration of protons in the reaction system is low.[11] This finding is consistent with reports that F^+ is an effective oxidant for Breslow-type enols or homoenolates, even under an inert atmosphere.[9,12] To address these issues, we propose introducing suitable proton- and fluorine-transfer agents, as well as NHC turnover agents, which might help accomplish a delicate kinetic balance for the desired β-protonation-α-fluorination cascade.

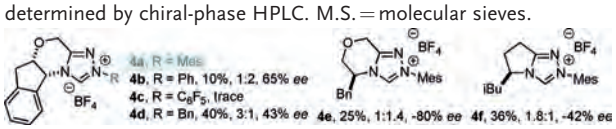
We began our investigation using cinnamaldehyde (**1a**) as the substrate. The lack of the second β-substituent makes this compound ideal for studying the α-fluorination step independently without concern about the asymmetric control of the β-protonation. A preliminary survey revealed that 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) is the preferred F^+ reagent for this transformation.[13] β-Fluorination and direct oxidation of the homoenolate are effectively suppressed as a result of the low solubility of Selectfluor in nonpolar solvents. Other, more soluble F^+ agents, such as *N*-fluorobenzene sulfonimide (NSFI), cause significant decomposition of **1a**. When small-sized primary alcohols are used as the catalyst turnover agent, premature esterification, yielding the nonfluorinated byproduct **3a′** (see Table 1), is the dominant reaction pathway. Bulkier secondary alcohols, such as cyclohexanol, lead to formation of the desired α-fluoro product **3a**, which is generated in low yield with high enantioselectivity (Table 1, entry 1). We believe lack of a proton-transfer promotor is responsible for the unproductive β-protonation. Significantly improved conversion was obtained when lithium isobutyrate (^{i}PrCO$_2$Li) was used (entry 2). It is hypothesized that ^{i}PrCO$_2$H is an effective proton source that accelerates β-protonation. The ^{i}PrCO$_2^-$ ion might also serve as a phase-transfer catalyst to assist solubilization of Selectfluor. Despite the dual role of ^{i}PrCO$_2$Li, **3a′** was still formed in 22% yield. Much higher chemoselectivity was observed when the solvent was changed from toluene to 1,4-dioxane, although the overall conversion decreased (entry 3). A control experiment, in which Selectfluor was absent, showed the β-protonation to be very slow in 1,4-dioxane, accounting for the poor conversion into **3a′**. Based on this result, we decided to examine conditions using solvent mixtures and further investigate various carboxylates (see Table S1 in the Supporting Information for more details). Eventually, the optimal reaction conditions were identified as those in entry 4, Table . A 4:1 mixture of toluene and 1,4-dioxane promotes high chemoselectivity, enantioselectivity, and yield. Screening of other NHC scaffolds results in compromised conversions and *ee* values (with cat. **4b–f**).

Table 1: Optimization of the reaction conditions for hydrofluorination of cinnamaldehyde.[a]



Entry	Solvent	Base	Yield [%]	**3a**/**3a′**	*ee* [%]
1	PhMe	K_2CO_3	12	5:1	88
2	PhMe	^{i}PrCO$_2$Li	93	3.3:1	92
3	1,4-dioxane	^{i}PrCO$_2$Li	34	33:1	93
4	PhMe/1,4-dioxane (4:1)	^{i}PrCO$_2$Li	86	17:1	96

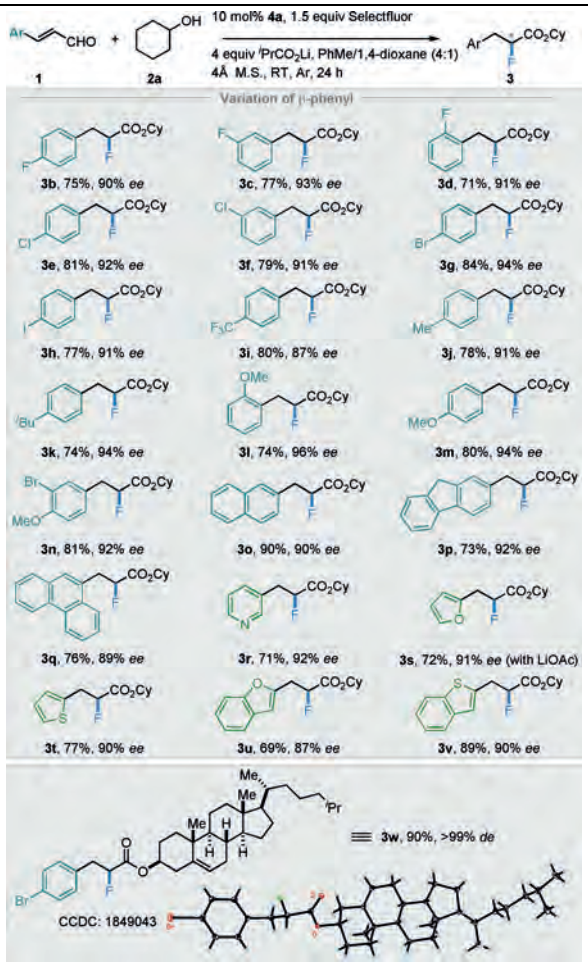
[a] Reactions were performed using 0.1 mmol of **1a** and 0.2 mmol of **2a** in 1.0 mL solvent under argon for 24 h at RT. Total yield for **3a** and **3a′** is given. Ratio of **3a** and **3a′** was determined by GC. The *ee* values were determined by chiral-phase HPLC. M.S. = molecular sieves.



The scope with respect to the β-aryl enals under the optimized reaction conditions was studied (Table 2). Both electron-poor and electron-rich substituents at various positions of the β-aryl group are well tolerated, and give the products **3a–n**. Minimal influence on yields and *ee* values was observed for *o*-substituted cinnamaldehydes, substrates that often perform poorly in homoenolate chemistry (**3d** and **3l**). The presence of higher ordered aryls with fused rings do not compromise the efficiency and selectivity of this reaction. Structurally appealing β-aryl-α-fluoroesters (**3o–q**) were obtained. Heteroaryl-containing substrates have been demonstrated only rarely in previous reports of olefin hydrofluorination. Electron-rich heteroarenes often compete for metal hydride addition, while those containing one or more basic nitrogen atoms bind to transition-metal catalysts. Our protocol can be applied to a wide range of β-heteroaryl compounds, and chiral α-fluoro esters with a β-pyridyl, furyl, benzofuryl, thienyl, or benzothienyl groups (**3r–v**) were formed with good yields and *ee* values. When cyclohexanol was replaced by cholesterol, the reaction proceeded in high yield and with exclusive diastereoselectivity (**3w**).

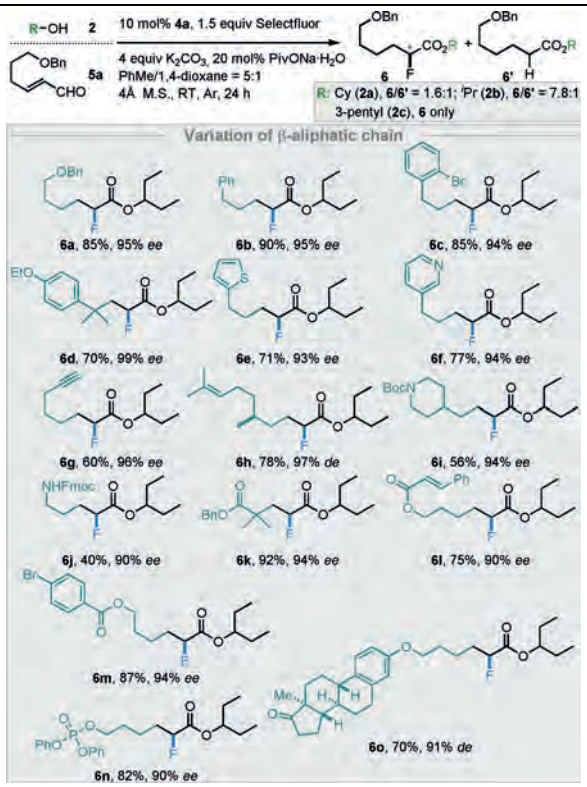
When the substrate scope is extended to β-alkyl enals, the chemoselectivity of hydrofluorination versus hydrogenation deteriorates considerably. Preliminary optimization of the reaction conditions showed that premature esterification competes with α-fluorination using cyclohexanol. Potassium carbonate, in combination with 20 mol% sodium pivalate as a dual protonation/fluorination buffer, leads to a mixture of the products **6** and **6′** in a ratio of 1.6:1 (Table 3). We tested bulky, acyclic secondary alcohols, hoping to further slow the esterification while maintaining good catalyst turnover. As expected, reactions using isopropyl alcohol significantly improved the ratio of **6**/**6′**, and with the bulkier 3-pentanol, **6** was formed exclusively. A series of β-alkyl enals were

Table 2: Scope with respect to β-aryl enals in the enantioselective hydrofluorination.



Yields are those for the isolated products and the *ee* values were determined by chiral-phase HPLC. Thermal ellipsoids for ORTEP structure shown at 50% probability.[16]

Table 3: Scope with respect to the β-alkyl enals in the enantioselective hydrofluorination.



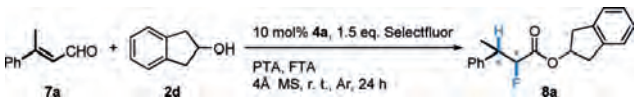
Yields are those for the isolated products and the *ee* values were determined by chiral-phase HPLC.

evaluated and generally, good yields and *ee* values were obtained (Table 3). Increasing steric bulk at the neighboring γ-carbon center does not affect the reaction efficiency and selectivity (**6d**). Alkyl chains containing a heterocyclic moiety, such as thiophene, pyridine, and piperidine, are well tolerated, giving the products **6e**,**f** and **6i**. A number of functional groups were introduced to the β-alkyl group, and showed no effect on the selectivity, giving the products **6g**–**o**. The reaction proceeds smoothly for enals with either a terminal alkyne or olefin (**6g** and **6h**), which often interfere with transition metal catalyzed reductive reactions. Despite the presence of two electrophiles in the reaction mixture, a number of nucleophilic groups are tolerated, and transesterification was not observed for substrates containing either an ester or phosphate moiety (**6k**–**n**). In cases in which the esterification used 3-pentanol, a number of side reaction pathways are suppressed. To demonstrate applicability to late-stage drug modification, an estrone analogue with a chiral fluorine-containing group (**6o**) was prepared in 70% yield and 91% *de*.

α-Fluoroesters containing two contiguous chiral centers are essential building blocks for synthetic and medicinal chemistry. Synthetic approaches to these molecules are rare.[14] Our hydrofluorination strategy offers a straightforward approach to α-fluoroesters with additional chiral centers from readily available β-substituted cinnamaldehydes. With these substrates, however, further challenges are presented. The rate of β-protonation might be affected by the extra β-substituent so that neither cyclohexanol nor 3-pentanol would be able to preclude the premature esterification. As expected, an inseparable nonfluorinated product (**8′**) was formed in significant quantities from reactions employing cyclohexanol and 3-pentanol. After further screening, it was found that 2,3-dihydro-1*H*-inden-2-ol (**2d**) is an excellent scavenger for NHC turnover, with little formation of **8′** (see Table S2).

After solving the chemoselectivity issue, diastereoselectivity appeared as a more serious problem. Although the NHC precursor **4** induces excellent discrimination in the α-fluorination step, asymmetric control of the β-protonation is likely to be compromised when a carboxylate is used as a proton-transfer agent. Our previous reports showed that only bridgehead nitrogen atoms can serve as highly enantioselective proton sources and low *ee* values were observed when carboxylate was used as a protonation promotor.[6] If the β-protonation occurs with low enantioselectivity for β,β-disubstituted enals, a mixture of diastereomeric products will

Table 4: Optimization of the reaction conditions for hydrofluorination of β-methyl cinnamaldehyde.[a]



Entry	Solvent	PTA	FTA (equiv)	Yield [%] (d.r.)	*ee* [%]
1	Conditions for Table 2			25 (1.4:1)	96
2	Conditions for Table 3			13 (1:1.2)	97
3	PhMe	quinuclidine	1-AdCO$_2$H (1.0)	30 (4:1)	98
4	PhMe	quinuclidine	1-AdCO$_2$H (1.0) + TFA (1.0)	53 (7:1)	>99
5[b]	mesitylene	quinuclidine	1-AdCO$_2$H (0.5) + TFA (1.0)	70 (>20:1)	>99

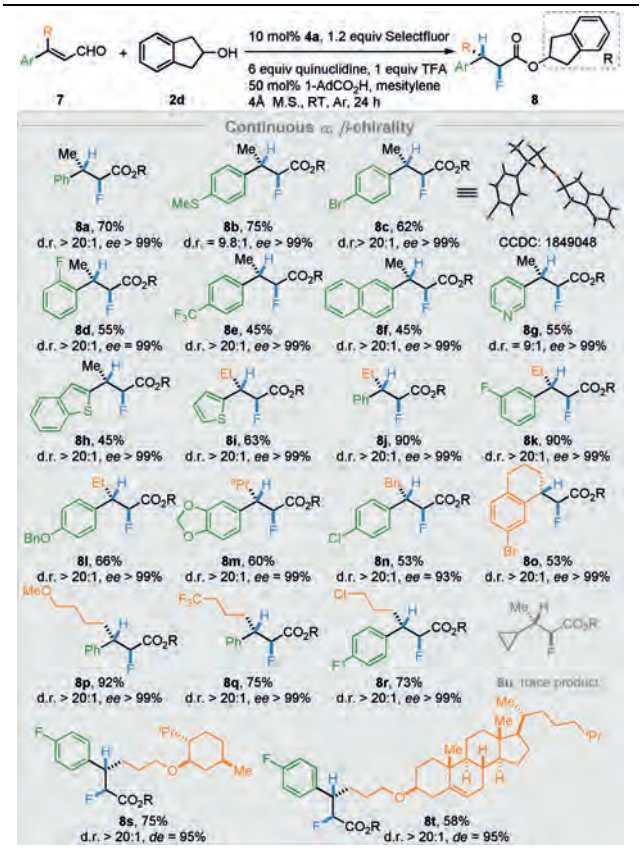
[a] Reactions were performed using 0.1 mmol **7a**, 0.25 mmol **2d**, 0.12 mmol Selectfluor, 0.6 mmol proton-transfer agent (PTA), and the indicated amount of fluorine-transfer agent (FTA) in 1.0 mL solvent at RT for 24 h. Yields determined by GC. The d.r. values were measured by ^{1}H NMR spectroscopy. The *ee* values were measured by chiral-phase HPLC. [b] The reaction was performed at 0 °C for 12 h and another 24 h at RT. TFA = trifluoroacetic acid.

be formed despite a highly selective α-fluorination event (Table 4). Indeed, the reaction involving β-methyl cinnamaldehyde yielded the desired hydrofluorination product **8a** in 25 % yield, 1.4:1 d.r. and 96 % *ee* using the optimized reaction conditions described in Table 2 (Table 4, entry 1). The reaction conditions used for Table 3 also lead to poor yield and d.r. (Table 4, entry 2). To address this issue, we decided to introduce two separate modifiers for β-protonation and α-fluorination, respectively. A combination of quinuclidine and carboxylic acid should be the most promising. Toste and coworkers reported carboxylic/phosphoric acids accelerate fluorine transfer from Selectfluoro by phase-transfer catalysis.[15] In this scenario, a proper choice of carboxylic acids may also facilitate highly selective α-fluorination. Compared to other carboxylic acids, 1-adamantanecarboxylic acid (1-AdCO$_2$H) quickly emerged as a superior fluorination promotor for this transformation. However, the overall yield of **8a** and the d.r. value remained unsatisfactory, and this can be attributed to the low acidity of 1-AdCO$_2$H, from which a proton is not fully transferred to quinuclidine (entry 3). As a result, the rate of β-protonation is attenuated and the enantioselectivity is compromised by direct, nonselective proton transfer from 1-AdCO$_2$H. To generate a sufficient concentration of protonated quinuclidine as the proton source, strong Brønsted acids were added and it was found that introduction of 1.0 equivalent of TFA simultaneously improved the yield and d.r. and *ee* values (entry 4). Performing the β-protonation at 0 °C and α-fluorination at room temperature led to hydrofluorined products with 70 % yield, greater than 20:1 d.r. and greater than 99 % *ee* (entry 5). The low temperature used for the β-protonation step enhances enantioselectivity and prevents destructive homoenolate oxidation. Both d.r. and *ee* values are significantly improved using the stepped temperature procedure, compared to room temperature only. (see Table S3 for more details)

The optimized reaction conditions are generally applicable for a broad scope of β,β-disubstituted enals (Table 5). Aromatic substitution, giving the products **8b**,**c** is widely tolerated for the β-aryl moiety. A decrease in the electron density of the β-aryl group resulted in diminished yield of the products **8d** and **8e** as well as d.r. values, probably because of the slow β-protonation. Substrates containing a β-heterocyclic group, especially those with basic nitrogen atoms, do not disrupt this delicate β-protonation-α-fluorination cascade (**8g–i**), and both the *ee* and d.r. values remain high. The β-methyl group can be extended to diverse aliphatic structures (**8j–n**). Enals with an exocyclic double bond react smoothly in good yield with excellent d.r. and *ee* values (**8o**). Functional groups, including labile halides on the β-alkyl chain, are not affected, yielding extra handles for further synthetic manipulations (**8p–r**). One limitation to this protocol is its failure with β-dialkyl enals. No desired hydrofluorination product was obtained when using cyclopropylideneacetaldehyde (**8u**). Compounds with elaborated β-alkyl groups, for example L-menthol and cholesterol, allow access to structurally complicated chiral α-fluoroesters (**8s**,**t**).

In summary, a general asymmetric hydrofluorination reaction of enals has been accomplished by NHC catalysis. This method represents a universal protocol for the synthesis of chiral α-fluoroesters from readily available enals. A dual

Table 5: Scope with respect to the β-alkyl-β-aryl enals in the diastereo- and enantioselective hydrofluorination.



Yields are those for the isolated products. The d.r. values were determined by ^{1}H NMR spectroscopy and the *ee* values were determined by chiral-phase HPLC.

promotor strategy is essential in the reaction to control the chemo-, diastereo-, and enantioselectivity. The key factor for this transformation lies in striking a balance between the relative rates of β-protonation and the subsequent α-fluorination. A number of side-reactions can be suppressed by an appropriate choice of modifiers. Carboxylates serve as a dual promotor for efficient asymmetric hydrofluorination of β-aryl and β-alkyl enals. Quinuclidine, TFA, and 1-$AdCO_2H$ are identified as competent additives for promoting reactions, involving the more challenging β,β-disubstituted enals, in good yields with excellent d.r. and *ee* values. The contiguous α- and β-chiral centers are dictated by a single NHC catalyst in two separate events.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · fluorine · N-heterocyclic carbenes · organocatalysis · reaction mechanisms

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