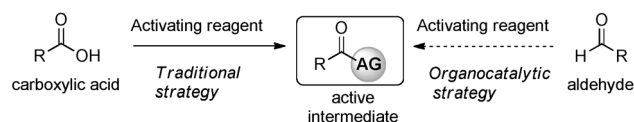**Cross-Coupling Reactions**

Organocatalytic Amidation and Esterification of Aldehydes with Activating Reagents by a Cross-Coupling Strategy**

Bin Tan, Narihiro Toda, and Carlos F. Barbas III*

Amide and ester functionalities are inarguably among the most abundant motifs in natural products, polymers, agrochemicals, and pharmaceuticals.[1] The development of synthetic routes to amides and esters have therefore attracted considerable interest.[2] Acylation of amines and alcohols with activated carboxylic acids is a common strategy, and the use of *N*-hydroxyimide esters as coupling intermediates has become the standard approach to amidation.[3] The traditional strategy involves direct coupling of carboxylic acids with *N*-hydroxyimides using carbodiimide activating reagents.[4] The by-product ureas formed may be difficult to remove and the most common coupling agent, *N,N'*-dicyclohexylcarbodiimide, is a potent allergen and sensitizer. Despite the remarkable generality of this reaction strategy, it suffers from both the industrial and green chemistry points of view. The development of effective and environmentally benign methods for this transformation under mild reaction conditions are needed.[5]

Cross-coupling amidation and esterification reactions of aldehydes are economically attractive alternatives to traditional synthesis.[6] However, the use of transition-metal catalysts[7] and the need for more than stoichiometric amounts of a hypervalent iodine (III) reagent[8] limit the practical application of this strategy. Quite recently, Wan and co-workers developed an *n*Bu4NI catalyzed amide formation reaction of aldehydes with *N,N*-disubstituted formamides.[9,10] Although only aromatic aldehydes are reactive and the reaction is limited to the formation of secondary amides from pre-formed formamides, the generation of an acyl radical from an aldehyde inspired us to develop an organocatalytic[11] approach to access versatile active intermediates which can be displaced in situ by amines or alcohols (Scheme 1).
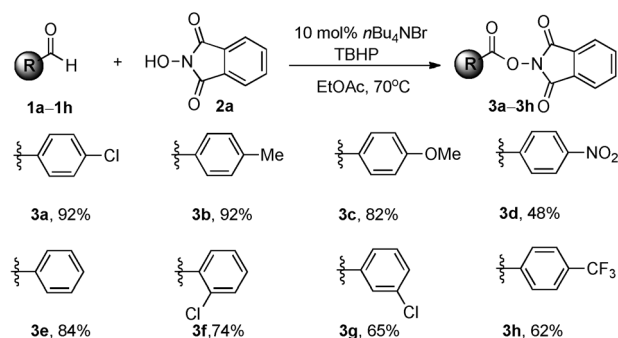
Our initial studies focused on the model reaction of 4-chlorobenzaldehyde **1a** with *N*-hydroxyphthalimide **2a** (NHPI).[12] With catalytic amounts of simple tetrabutylammonium iodide (*n*Bu4NI) as the precatalyst and a solution of *tert*-butyl hydrogen peroxide (TBHP) in decane as co-oxidant at room temperature, the desired active 4-chlorobenzoate

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Scheme 1. Comparison of the traditional strategy to synthesize an active intermediate from an acid verses organocatalytic cross-coupling using an aldehyde (AG = activating group).

ester **3a** was isolated in 35% yield (see Table 1 in the Supporting Information for optimization details). When the reaction temperature was increased to 70°C, the obtained yield was 83%. Among the catalysts screened, several were very effective. The cross-coupling reaction was most effective in the presence of *n*Bu4NBr, indicating that the iodide was not essential for the reaction. To the best of our knowledge, this is the first example of the use of ammonium bromide as a catalyst for a coupling reaction.[13] The desired product was not formed in the absence of a catalyst or oxidant. The presence of water was detrimental, as the yield was significantly higher when TBHP in decane was used as an oxidant rather than when an aqueous solution of TBHP or aqueous H_2O_2 was used. Further optimization involved the study of catalyst loading and a solvent screen. The optimal reaction conditions found consisted of ammonium iodide or bromide (10 mol%) and TBHP (2 equiv), with ethyl acetate as the solvent. NHPI could be replaced with N-hydroxysuccinimide (NHSI, **2b**) under identical conditions to provide the corresponding active ester **4a** in a comparable yield.

To examine the scope of this transformation, the optimized conditions were applied to the reactions of a variety of aldehydes (**1**) with **2a**. As shown in Scheme 2, the electronic properties and positions of the aromatic ring substituents had

Scheme 2. Scope of the reaction of aldehydes with NHPI (**2a**) catalyzed by *n*Bu4NBr.

a strong effect on reactivity when using *n*Bu$_4$NBr as a catalyst, and yields ranged from 48% to 92%.

When *n*Bu$_4$NI was used as the catalyst, the same reactions afforded the desired products in reasonable to excellent yields upon isolation (Scheme 3). With *n*Bu$_4$NI as the catalyst,
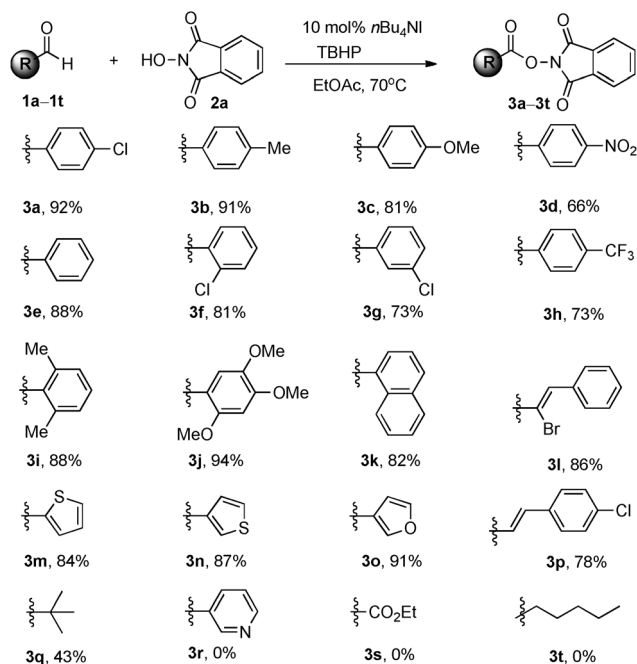
Scheme 3. Scope of the reaction of aldehydes with NHPI (**2a**) catalyzed by *n*Bu$_4$NI.

electron-rich aromatic substrates again provided higher yields than electron-poor aromatic aldehydes. Reactants with heteroaromatic groups such as furyl and thienyl also afforded the desired products (**3m**, **3n**, and **3o**) in excellent yield. Furthermore, conjugated aldehydes were also suitable reaction partners and gave rise to the corresponding active esters **3l** and **3p** in good yields. Notably, alkyl aldehydes were not reactive, which suggests that an aromatic functionality is required to stabilize the active species. The method was successfully extended to *N*-hydroxysuccinimides as reactants (Scheme 4). In support of the utility of this method, we
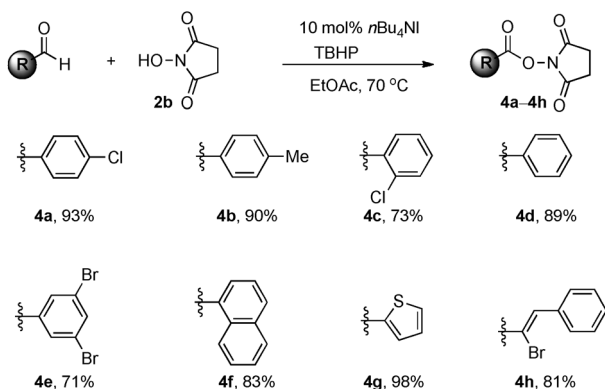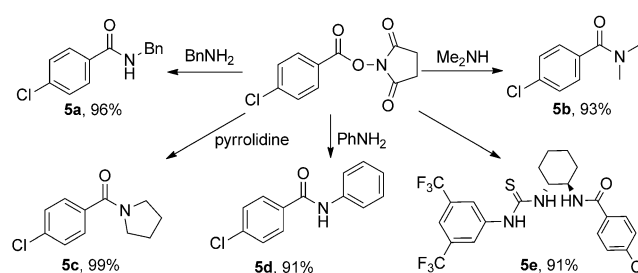
Scheme 4. Scope of the reaction of aldehydes with NHSI (**2b**) catalyzed by *n*Bu$_4$NI.
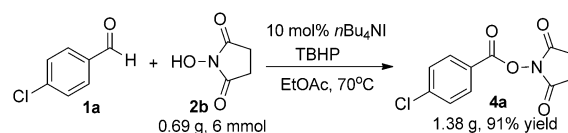
**Scheme 5.** Preparative scale experiment.

conducted the reaction on a gram scale, whereupon the product was obtained with almost no change in yield (Scheme 5).

Next, we examined the amine displacement step. A broad range of amides was obtained following the addition of primary and secondary amines and anilines. In the case of amines with stereocenters, the optical purity was maintained and organocatalyst **5e** was obtained in high yield (Scheme 6).[14] We then investigated the feasibility of a one-

Scheme 6. Synthesis of various amides.

pot transformation of aldehydes into amides. When benzylamine was added to the reaction mixture of aldehyde and NHSI, we discovered that the desired products were readily obtained in good yields (Scheme 7). It is noteworthy that the free amine can be used directly, formation of the amine salt was not required.
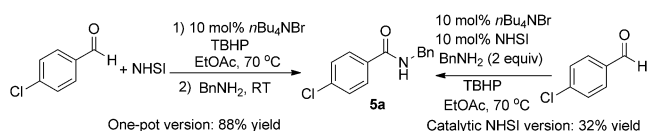
Scheme 7. One-pot synthesis of an amide and the use of *N*-hydroxyimide as a co-catalyst. For procedures, see the Supporting Information.

In these transformations, *N*-hydroxyimide could be recovered unmodified. Thus, we envisioned that only catalytic amounts of *N*-hydroxyimide should be needed for these cross-coupling reactions. Using our established reaction conditions, but with only 10 mol% of NHSI, we were able to realize this catalytic version, however, the yield was low (32%; Scheme 7).

To investigate the potential use of our cross-coupling reaction to synthesize other active esters, we chose to study its utility in the synthesis of hexafluoroisopropyl alcohol (HFIP) esters. The side product of amide bond formation with HFIP

esters is HFIP, which is readily removed by simple evaporation. HFIP esters are practical for industrial-scale syntheses.[15] Therefore, we investigated the feasibility of the cross-coupling of 4-chlorobenzaldehyde with HFIP. The reaction mixture was treated with benzylamine and stirred at room temperature for 12 h. The desired product was obtained in 48% yield. After further optimization of the reaction conditions (see the Supporting Information), the yield was improved to 92%. As shown in Scheme 8, the substrate scope was general in terms of aromatic aldehydes.
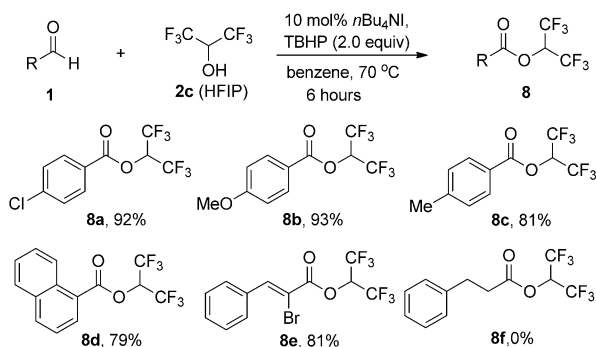

Scheme 8. Scope of the cross-coupling reaction involving HFIP.

Based on a recent report that the reagent *N*-fluorobenzenesulfonimide (NFSI) can readily form fluorine and sulfonamide radicals,[16] we hypothesized that cross-coupling of aldehydes with NFSI could generate a new type of active intermediate (**9a**) for the formation of amides and esters. An initial study was performed using 4-chlorobenzaldehyde and NFSI in the presence of 30 mol% *n*Bu$_4$NI [Scheme 9, Eq. (1)]. The expected product was produced with 32% yield and further transformed into an amide in almost quantitative yield upon treatment with benzylamine. Subsequent study with the NFSI precursor benzenesulfonimide revealed that it was effective, thus indicating that the fluorine was not required for the reaction. To improve the yield, we then tested different sulfonimides [Scheme 9, Eq. (2)]. The electronic properties and steric bulk of the substrates influenced the reactivity. The simple dimethylsulfonimide proved to be the best in terms of reactivity and chemical yield. The yield was increased to 85% after additional optimization (for details, see the Supporting Information). As we expected, active intermediate **9e** was effective in synthesizing amides and esters without the need for a base [Scheme 9, Eq. (3)]. The amidation reactions were complete after only 10 min under ambient conditionsn and provided primary or secondary amide products in quantitative yield. Substrates were, however, limited to aromatic aldehydes. These bench-stable active imides provide new opportunities in synthesis that remain to be fully explored.

A proposed reaction mechanism which is consistent with both additional mechanistic studies (see the Supporting Information) and our use of NHPI, NHSI, HFIP, and sulfonimides is presented in Scheme 10. Initially, *n*Bu$_4$NI is oxidized by TBHP to generate the active intermediate iodide
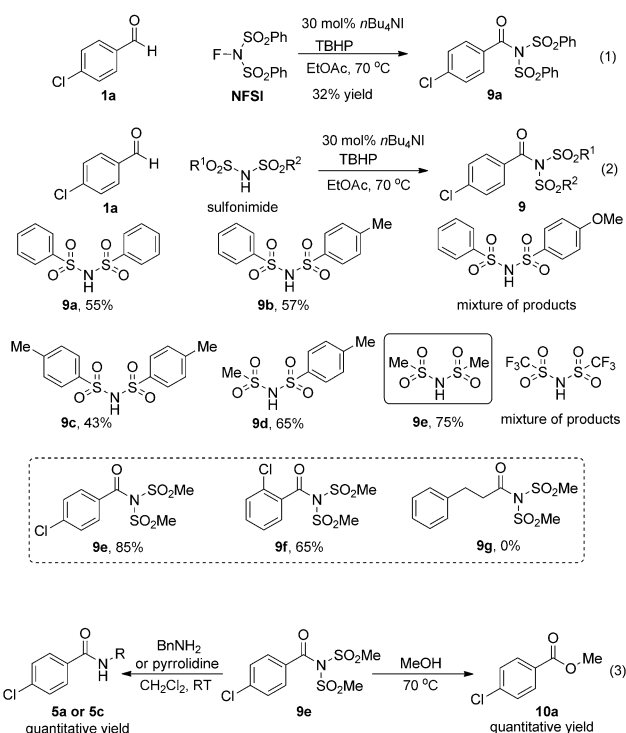
Scheme 9. Discovery of new active imide reagents for amide and ester synthesis.
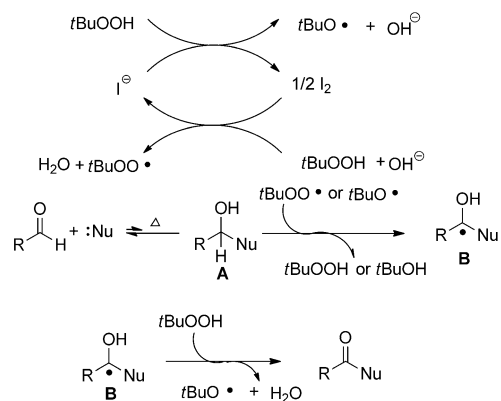
Scheme 10. Proposed reaction mechanism.

and the *tert*-butoxyl and *tert*-butylperoxyl radicals. These radicals subsequently abstract a hydrogen atom from the acetal or aminal species **A**, which forms from the reaction of the nucleophiles with the aldehyde, and the resulting radical species **B** is then further oxidized to the product esters or imides. The oxidation of **B** might occur either through a single-electron transfer reaction to *t*BuOOH directly or after its deprotonation to the radical anion. We cannot rule out the role of an iodine radical as an active species. To examine this mechanism, we studied the formation of methyl esters under the same reaction conditions. We found that methyl esters could only be formed when acid (*p*TsOH) was added to facilitate acetal formation. Note that NHPI, NHSI,

HFIP, and sulfonimides are all significantly more acidic than methanol, and that acetal/aminal formation is possible in these cases without the addition of an acid catalyst. The lack of methyl ester formation in the absence of an acetalyzation catalyst reduces the likelihood of acyl iodide or acyl radical intermediates as key reactive species. Our mechanism is significantly different from the one proposed by Wan and co-workers[9] for their reaction, wherein the product is formed by the intermolecular reaction of acyl and aminyl radicals. Our mechanism is, however, consistent with the detection of an acetal radical in a recent study concerning hypervalent-iodine-based coupling.[17] See the Supporting Information for a more detailed discussion of the reaction mechanism.

In summary, we have developed an organocatalytic cross-coupling reaction of aldehydes with N-hydroxyimides, hexafluoroisopropyl alcohol, and sulfonimides that provides active esters and imides in moderate to excellent yields. The resulting active intermediates can be directly converted into amides or esters in one pot. The straightforward process described here is simple, highly effective, and makes use of readily available starting materials, all of which should render this method attractive to synthetic chemists. The newly discovered active imide reagents will likely be useful for amide and ester formation, and the use of ammonium bromide salts should facilitate the development of a wide range of radical reactions. Investigations into the reaction mechanism, and the expansion of this chemistry to other transformations, are currently underway in our laboratory.

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