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Enantioselective Intermolecular Enamide–Aldehyde Cross-Coupling Catalyzed by Chiral *N*-Heterocyclic Carbenes

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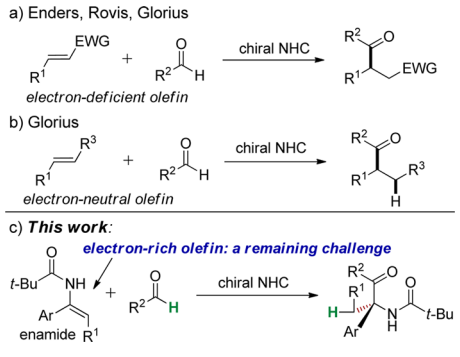
Supporting Information

ABSTRACT: The unprecedented *N*-heterocyclic carbene (NHC)-catalyzed intermolecular cross-coupling of enamides and aldehydes is described. Upon exposure of enamides to aldehydes in the presence of a NHC catalyst, catalytic C–C bond formation occurs, providing highly enantioselective *N*-protected amines, bearing a quaternary carbon center, in good yields and with high enantioselectivities.

Acyl anion equivalents generated from the reaction of aldehydes with *N*-heterocyclic carbenes (NHCs) offer an elegant access to a wide range of organic transformations.[1] In this regard, NHC-catalyzed additions of aldehydes to Michael acceptors have been extensively studied.[2] Examples of intramolecular asymmetric addition reactions of aldehydes to various olefins have been reported by Enders,[3a] Rovis,[3b,e] Miller,[3d] Glorius,[3f,h−m] and other groups.[3c] In another direction, intermolecular addition reactions have also received intense attention in the past few years.[4] The first moderately to highly enantioselective intermolecular Stetter reactions were reported by the research groups of Enders[4a,b] and Rovis[4c−e] (Scheme 1a).

Scheme 1. NHC-Catalyzed Cross-Couplings of Aldehydes and Olefins

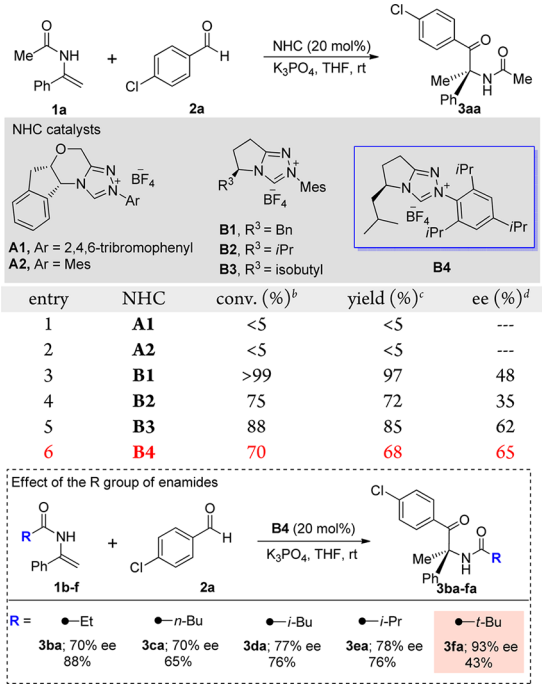


More recently, Rovis[4f,g] and Glorius[7] independently reported several attractive examples of highly enantioselective additions of aldehydes to electron-deficient olefins. Impressively, Glorius et al. recently described an NHC-catalyzed intermolecular enantioselective addition of aldehydes to electron-neutral olefins (Scheme 1b, cyclopropenes as olefins).[5]

Although olefins represent versatile synthetic building blocks, the properties of electron-rich olefins have rarely been exploited in NHC-catalyzed cross-coupling reactions. Herein we report an enantioselective intermolecular addition of aldehydes to electron-rich enamides,[6] resulting in the formation of valuable *N*-acyl-protected amine derivatives in good yields and with high enantioselectivities (Scheme 1c).[7]

Key results of optimization are summarized in Table 1 (see Supporting Information for details). We chose enamide **1a** and aldehyde **2a** as the model substrates. Given the importance of chiral catalysts in asymmetric transformation, we briefly surveyed the indanol-derived triazolium catalysts.[8] As highlighted in Table 1, catalysts **A1** and **A2** did not participate in the reaction (entries 1 and 2). Other NHCs showed moderate levels of either reactivity or selectivity (entries 3 and 4). The *N*-mesityl (*N*-Mes)

Table 1. Optimization[a]



entry	NHC	conv. (%)[b]	yield (%)[c]	ee (%)[d]
1	**A1**	<5	<5	---
2	**A2**	<5	<5	---
3	**B1**	>99	97	48
4	**B2**	75	72	35
5	**B3**	88	85	62
6	**B4**	70	68	65

[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), NHC (20 mol %), K_3PO_4 (2.0 equiv), THF (1.0 mL), room temperature, argon atmosphere, 48 h. [b]The conversion of **1a** was determined by crude ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c]Yield of isolated product. [d]The ee value was determined by HPLC analysis on a chiral stationary phase.

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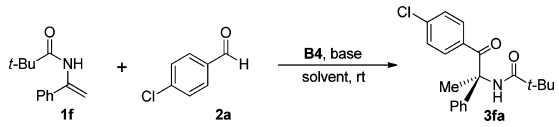
substituent was proven to be especially valuable for catalyst performance. We were pleased to find that *N*-Mes-substituted catalyst **B3** afforded the desired product **3aa** in 75% yield with 62% ee (entry 5). Finally, the most efficient catalyst was identified as **B4**, containing an isobutyl substituent and an *N*-2,4,6-(iPr)$_3$C$_6$H$_2$ group (entry 6, 65% ee). With the identification of a suitably reactive catalyst system, we began to investigate the effect of an R substituent on enamide substrate (Table 1, **3ba**–**3fa**). Notably, when enamide **1f**, containing a bulky *tert*-butyl amide substituent, was used, 93% ee was obtained but with a moderate yield (43%).

Solvent and base screening showed that a combination of solvent/base was beneficial to this reaction (Table 2, entries 5 and 6). Finally, optimization of several reaction parameters, including the concentration of the reactant, the catalyst loadings, and the reaction time (entries 7–13), revealed that product **3fa** could be obtained in the highest yield and ee when the reaction of **1f** was conducted with 1.5 equiv of **2a** and 15 mol% catalyst **B4** in MTBE at room temperature for 24 h (entry 13).

Table 2. Further Optimization[a]

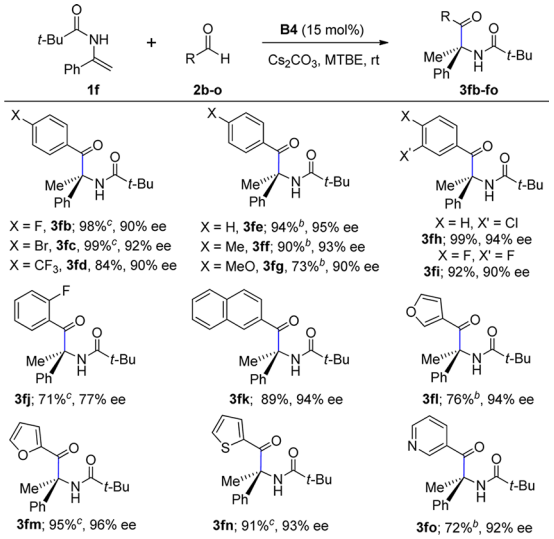


entry	solvent	base	time (h)	yield (%)[b]	ee (%)[c]
1	1,4-dioxane	K_3PO_4	48	<5	N.D.
2	toluene	K_3PO_4	48	39	90
3	DCM	K_3PO_4	48	23	86
4	$CHCl_3$	K_3PO_4	48	<5	N.D,
5	iPr_2O	K_3PO_4	24	99	91
6	MTBE[e]	K_3PO_4	24	98	92
7[d]	MTBE[e]	K_3PO_4	48	68	92
8	MTBE	KH_2PO_4	24	<5	N.D.
9	MTBE	CsOAc	24	<5	N.D.
10	MTBE	$KHCO_3$	24	<5	N.D.
11	MTBE	Li_2CO_3	24	<5	N.D.
12	MTBE	Cs_2CO_3	24	99	92
13[f]	MTBE	Cs_2CO_3	24	92	92

[a]Reaction conditions: **1f** (0.1 mmol), **2a** (0.15 mmol), **B4** (20 mol%), base (2.0 equiv), solvent (1.0 mL), room temperature, argon atmosphere, 24–48 h. [b]Yield of isolated product. [c]The ee value was determined by HPLC analysis on a chiral stationary phase. [d]10 mol% of **B4** was used. [e]MTBE = methyl *tert*-butyl ether. [f]15 mol% of **B4** was used.

With the advent of this efficient catalytic system, we then examined the scope of this transformation (Tables 3 and 4). A number of aryl aldehydes were tested and gave the corresponding products in good yields with high enantioselectivities (Table 3, **3fb**–**3fo**). In contrast, alkyl aldehydes indicate poor reactivities. Enamides were next investigated. As shown in Table 4, various substituents on the aryl ring (R^1), both electron-donating and electron-withdrawing, are compatible with the reaction conditions, and the products were obtained in good yields with high ee's (**3ia**–**3ua**). Notably, products bearing two heteroaryls could also be achieved in good yields and with excellent enantioselectivities (**3tm** and **3wm**). Substituted enamides (**4a**–**4i**) were also tested and afforded desired products in moderate to good yields and high ee's (Table 5). It should be stressed that the reaction of cyclic enamide **4i** with aldehyde **2m** proceeded in high enantioselectivity (**5im**). The absolute configuration of **3sf** was unequivocally determined by single-crystal X-ray diffraction (Supporting Information).[9]

Table 3. Scope of Aldehydes[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15–0.20 mmol), **B4** (15 mol %), Cs_2CO_3 (2.0 equiv), MTBE (1.0 mL), room temperature, argon atmosphere, 24–48 h. [b]**1** (0.15 mmol), **2** (0.1 mmol), **B4** (20 mol%), Cs_2CO_3 (3.0 equiv), iPr_2O (1.0 mL) were used. [c]iPr_2O as solvent.

Our proposed mechanism is illustrated in Scheme 2. Addition of NHC precatalyst **B4** to aldehyde **2** yields an NHC-bonded Breslow intermediate **I**.[10] The Breslow intermediate **I** then undergoes a cross-coupling with enamide **1**, eventually resulting in product **3**. To further clearly understand the reaction mechanism, a plausible transition state is depicted in Scheme 2. We suggest that the push–pull nature of Breslow intermediate **I** promotes the formation of a reverse Cope elimination-like transition state[11,13,14] (Scheme 2). This concerted mechanism was first proposed by Glorius[3g] and supported by a detailed DFT calculation later.[3i,k,13] It is notable that a similar mechanism has also been proposed to explain a Stetter reaction reported by Rovis et al.[12] The favored and disfavored transition-state models are proposed in Scheme 2b,c. There is no doubt that the orientation of enamide plays a vital role in steric control. While the bulkier pivaloyl amide unit appears in the proximal position of the *N*-(iPr)$_3$Ph unit (*N*-Mes) (Scheme 2c), the steric crowding that is created may lead to destabilization of the transition state.

To further support our mechanistic hypothesis, several additional experiments were conducted. As indicated in eq 1, the absence of acidic N–H in enamide **6** leads to failure of the reaction. We speculate that the N–Me substituent of **6** suffers from strong destabilizing interactions with the isobutyl or other substituents on the catalyst. Another important issue may be the tautomerization between enamide **1** and *in situ*-formed imine **1′**, which could serve as the electrophile for the net transformation (Scheme 2a). In 2005, the Miller group uncovered an impressive intermolecular aldehyde–imine cross-coupling reaction via thiazoylalanine-catalyzed aza-benzoin strategy.[15] We conducted a similar experiment with imine **8** and aldehyde **2a**. As shown in eq 2, no desired product **9** was detected under standard conditions, which indicates that the aza-benzoin reaction mechanism might not be preferred in our reaction. Moreover, the labeling experiment with **1f** demonstrates that the enamide is the major form relative to its tautomer imine (eq 3). Although partial deuterium transfers are detected in product **3fc** (eq 4, 70% D), we deduce that this phenomenon does not conflict with our

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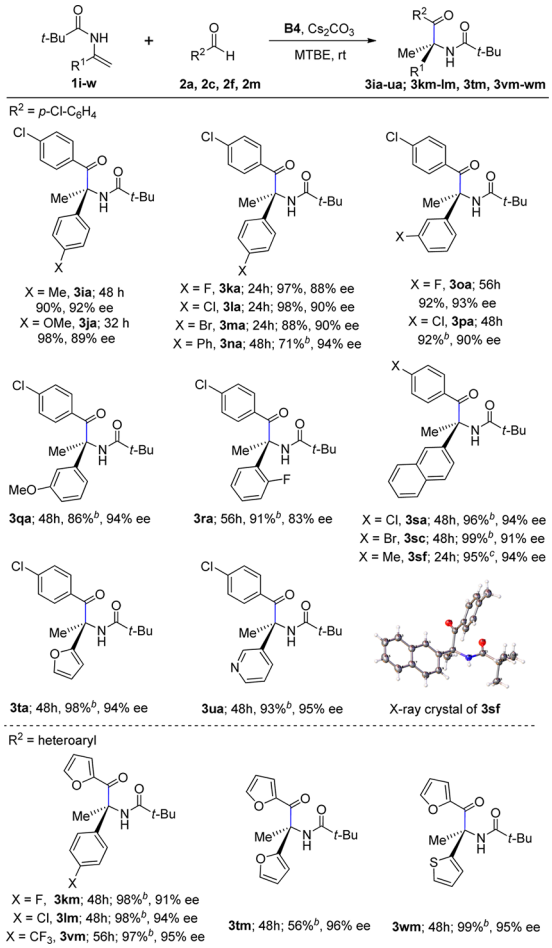
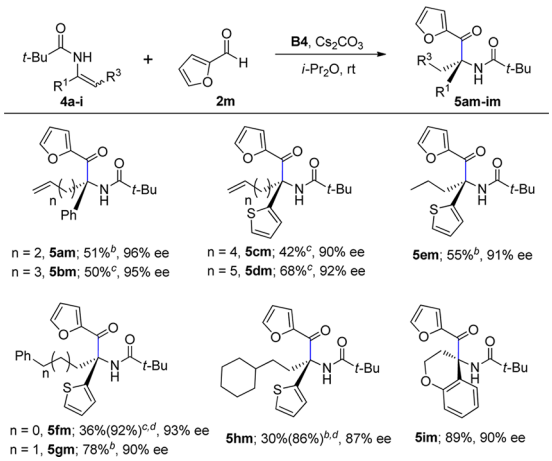
Table 4. Scope of Enamides[a]



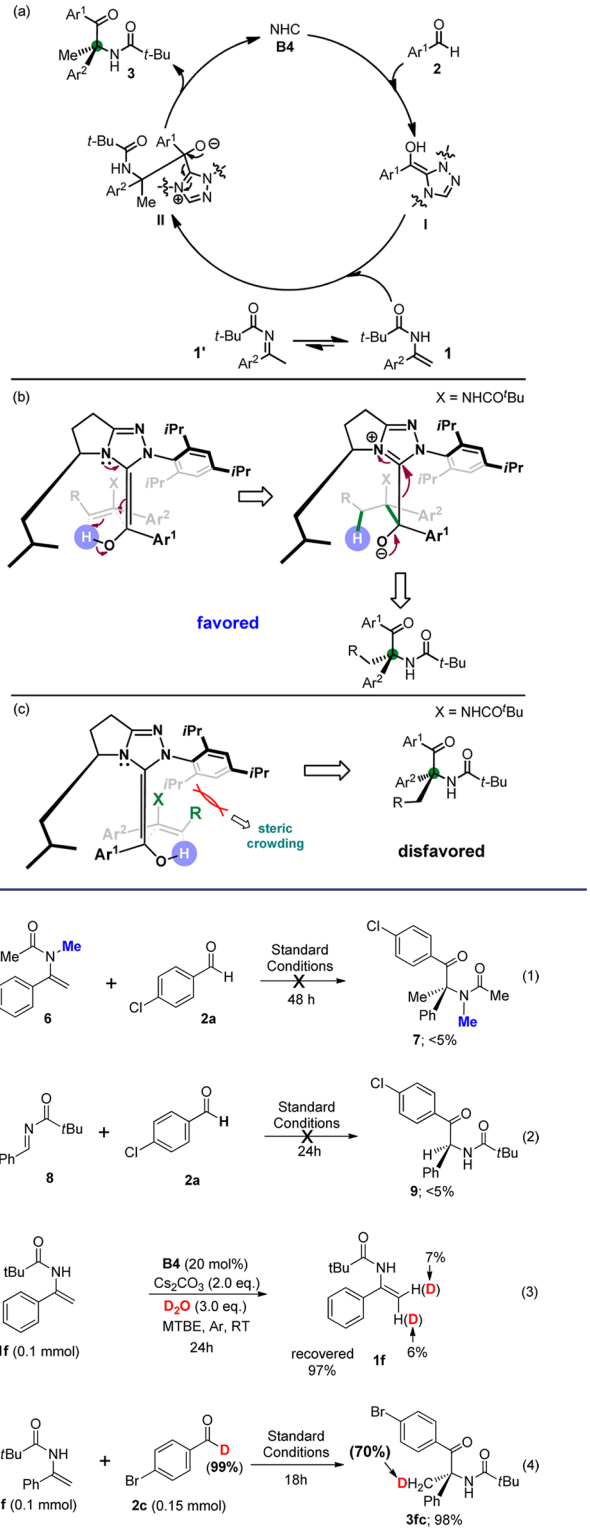
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15–0.20 mmol), **B4** (15 mol %), Cs_2CO_3 (2.0 equiv), MTBE (1.0 mL), room temperature, argon atmosphere, 24–56 h. [b]iPr_2O as solvent. [c]**1** (0.15 mmol), **2** (0.1 mmol), **B4** (20 mol%), Cs_2CO_3 (3.0 equiv), iPr_2O (1.0 mL) were used.

Table 5. Further Scope of Enamides[a]



[a]Reaction conditions: **4a–4i** (0.10 mmol), **2m** (0.20 mmol), **B4** (20 mol%), Cs_2CO_3 (2.0 equiv), iPr_2O (1.0 mL), room temperature, argon atmosphere, 72 h. [b]*E*-configuration of **4**. [c]*Z*-configuration of **4**. [d]Yield based on recovery of **4**.

Scheme 2. Proposed Mechanism and Transition-State Models



proposed concerted mechanism. A plausible reason is that the Breslow intermediate itself introduces an exchangeable O–D group that could place D where it ends up in 70% of product **3fc** (eq 4). Probably, the 30% of H in product **3fc** may also come from enamide exchange in a bimolecular fashion. Nevertheless, building upon current experimental evidence, the tautomerization–aza-benzoin mechanism still cannot be completely ruled out.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13501.

X-ray crystallographic data for **3sf** (CIF)
Experimental procedures, characterization data, and NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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