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N-Heterocyclic Carbene-Catalyzed Amidation of Unactivated Esters with Amino Alcohols

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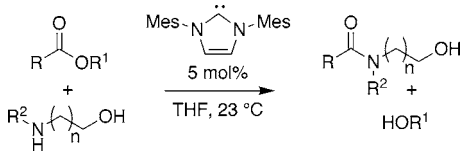
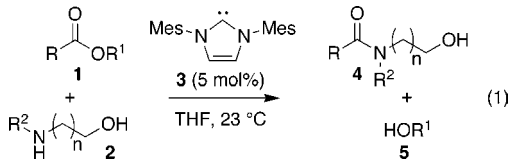
ABSTRACT



A catalytic amidation of unactivated esters with amino alcohols is described. A series of solution studies in addition to the first X-ray structure of a carbene–alcohol complex support a carbene-base nucleophile activation mechanism.

Synthesis of amides is important in many areas of chemistry, including peptide, polymer, and complex molecule synthesis.[1] Condensation products of optically active amino alcohols and carboxylic acids are of particular significance due to their impact in stereoselective synthesis.[2] Dehydration (and oxidation) of *N*-hydroxyalkyl amides affords valuable heterocycles that are present in many biologically active natural products.[3] Mild methods for the synthesis of amides rely on activation of carboxylic acid derivatives using stoichiometric quantities of condensation or activating reagents.[1] Direct coupling of amines and alcohols with unactivated carboxylic acid derivatives is of current interest.[4] Herein, we report the development of a carbene-catalyzed amidation of unactivated esters with amino alcohols (eq 1). Additionally, we describe preliminary mechanistic studies that suggest an uncharted mode of catalysis for stable carbenes via a carbene−alcohol hydrogen-bond interaction.



The discovery of stable nitrogen-heterocyclic carbenes (NHCs)[5] has had a significant impact on the development of new methodologies for organic synthesis.[6] NHCs have served both as ligands in organometallic catalyst systems[7]

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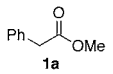
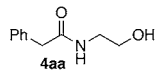
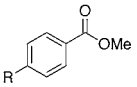
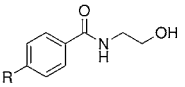
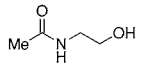
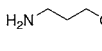
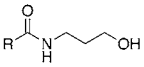
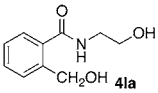
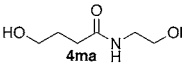
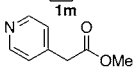
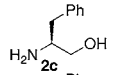
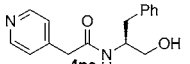
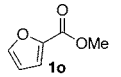
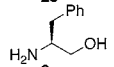
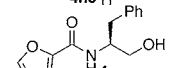
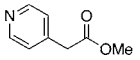
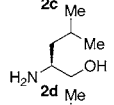
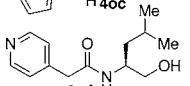
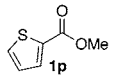
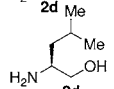
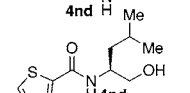
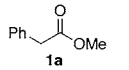
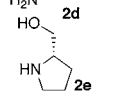
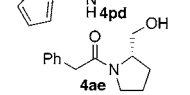
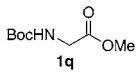
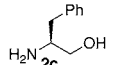
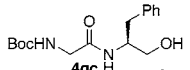
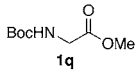
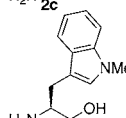
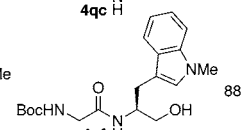
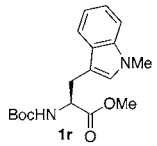
and as organic catalysts.[8] Furthermore, fascinating reports regarding the use of NHCs as nucleophilic catalysts[9] for polymerization of lactones and transesterification reactions have appeared.[10]

As part of a program directed at the discovery of new and efficient methods for target-oriented synthesis, we sought the development of a single-step and catalytic amidation of unactivated esters. In preliminary studies focused on carbene-catalyzed amidation of esters, we discovered that amino alcohols were particularly reactive. A combination of superb reactivity, ready availability, and ease of storage of *N*,*N*-bismesitylimidazolylidene[5b] (**3**, IMes) led to its selection as the catalyst for our amidation studies. Under optimal conditions (tetrahydrofuran, 1.0 M initial concentration of substrates, 23 °C), treatment of an equimolar amount of an amino alcohol and an unactivated ester with IMes (**3**, 5 mol %) affords the corresponding amide in high yield (Table 1). Under standard conditions, the coupling of methyl phenylacetate (**1a**) and ethanolamine (**2a**) was complete in 8 h, while the corresponding reaction with methyl benzoate (**1b**) gave the desired amide in 75% yield after 24 h (Table 1, entries 1 and 2, respectively).[11]

Both aromatic and aliphatic esters with a wide range of functional groups may be employed in this amidation reaction. The amidation reaction is sensitive to both electronic and steric factors (Table 1, entries 2−7 and 8−11, respectively).[12] The presence of heterocycles is tolerated both on the ester and the amino alcohol components (Table 1, entries 16−19 and 22−23, respectively). The IMes (**3**)-catalyzed

Table 1. Catalytic Amidation of Esters with Amino Alcohols

entry	ester	amino alcohol	amide	yield (%)[a]
1	 **1a**	 **2a**	 **4aa**	100 (96)[b]
2	 **1b**, R = H	 **2a**	 **4ba**, R = H	75 (94)[c]
3	**1c**, R = COMe		**4ca**, R = COMe	87
4	**1d**, R = CN		**4da**, R = CN	96
5	**1e**, R = CF_3		**4ea**, R = CF_3	95
6	**1f**, R = F		**4fa**, R = F	88
7	**1g**, R = OMe		**4ga**, R = OMe	31 (69)[c]
				
8	**1h**, R = Me	**2a**	**4ha**	99
9	**1i**, R = Bn			95
10	**1j**, R = *i*Pr			34
11	**1k**, R = *t*Bu			0
				
12	**1a**, R = CH_2Ph	**2b**	**4ab**, R = CH_2Ph	99
13	**1b**, R = Ph		**4bb**, R = Ph	16 (96)[c]
14	 **1l**	 **2a**	 **4la**	66
15	 **1m**	 **2a**	 **4ma**	88
16	 **1n**	 **2c**	 **4nc**	86
17	 **1o**	 **2c**	 **4oc**	89
18	 **1n**	 **2d**	 **4nd**	84
19	 **1p**	 **2d**	 **4pd**	77
20	 **1a**	 **2e**	 **4ae**	99
21	 **1q**	 **2c**	 **4qc**	83
22	 **1q**	 **2f**	 **4qf**	88
23	 **1r**	**2c**	**4rc**	88[d]

[a] Reaction times 1.5−24 h; isolated yield after purification. [b] In situ generation of IMes (6.5 mol % IMes·HCl, 5.0 mol % ^{t}BuOK). [c] Anhydrous LiCl (5 mol %) used as an additive. [d] >94% de, >98% ee.

(5) For the first successful isolation of an NHC, see: (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361−363. (b) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1992**, *114*, 5530−5534. For early studies, see: (c) Wanzlick, H.-W.; Schikora, E. *Angew. Chem*. **1960**, *72*, 494. (d) Wanzlick, H.-W.; Kleiner, H.-J. *Angew. Chem*. **1961**, *73*, 493.

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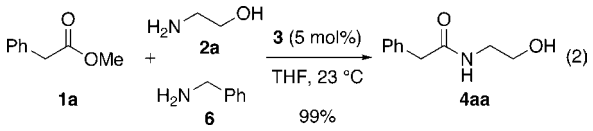
(11) (a) In the absence of **3**, incubation of equimolar amounts of esters **1a** and **1b** with **2a** at 23 °C provides less than 2 and 1%, respectively, of the corresponding amides in 12 h. (b) The use of sodium methoxide and potassium ^{t}butoxide in place of IMes (**3**) in the coupling of **1a** and **2a** gave 60 and 74% yield of **4aa**, respectively. See Supporting Information.

(12) Introduction of anhydrous lithium chloride (5 mol %) to the reaction mixture increases the rate of this coupling (Table 1, entries 2, 7, and 13).

condensation of optically active *N*-Boc-1-methyl-L-tryptophan methyl ester and L-phenylalaninol provided the corresponding amide in good yield (Table 1, entry 23).[13] This catalytic amidation reaction does not require use of excess coupling components, heat, vacuum, molecular sieves, or activated esters for completion.[10] The high reactivity of amino alcohols can be used to an advantage in their selective coupling with unactivated esters in the presence of amines (eq 2).

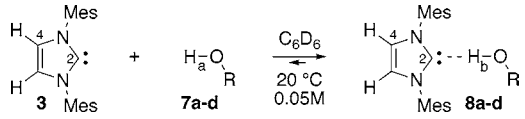


Significantly, this amidation reaction proceeds with equal efficiency when a solution of catalyst, IMes (**3**), is prepared by the addition of potassium *tert*-butoxide (5 mol %) to a suspension of *N*,*N*-bismesitylimidazolium chloride (6.5 mol %) in tetrahydrofuran (Table 1, entry 1).[10c,d] This method is particularly effective for use of NHCs that are more difficult to isolate.[14] Despite the clear practical advantage of using in situ-generated carbene samples, we have relied on recrystallized samples of IMes (**3**) in these preliminary studies to allow thorough mechanistic investigation.

These carbene catalysts have been previously proposed to act as nucleophilic catalysts in transesterification reactions (through activated C2-acylimidazolium intermediates).[10a−f,15] However, our observations regarding the surprising stability of carbene−alcohol complexes prompt consideration of an additional mode of catalysis for NHCs. Mixing an equimolar amount of IMes (**3**) and anhydrous methanol (**7b**) in C_6D_6 (0.05 M, 20 °C) leads to immediate formation of *N*,*N*-bismesityl-imidazolylidene−methanol complex **8b** (Table 2, entry 2).[16] The hydroxyl proton of complex **8b** displays a significant downfield shift in the ^{1}H NMR spectrum (Table 2, entry 2).[17] Significantly, the C2 resonance of complex **8b** at 209.7 ppm is upfield by 9.7 ppm as compared to the C2 resonance of carbene **3**.[18] We have also prepared the hexadeuterated variant of this complex, IMes-d_2−methanol-d_4 (**8b**-d_6),[14] that displays a C4 resonance (δ 121.1, triplet, J^1_{CD} = 27.0 Hz) and a C2 resonance (δ 203.9, singlet) in C_6D_6, most consistent with an imidazolylidene-d_2 fragment rather than an imidazolium-d_3 substructure.[19] The hydroxyl proton of other alcohols, including ^{t}butanol, ethanolamine, and benzyl alcohol, display a similar downfield shift upon complex formation with IMes (Table 2).[20] Samples containing unequal ratios of IMes to alcohol(s) exhibit averaged resonances suggesting dynamic systems with exchange rates faster than the NMR time scale. Benzylamine does not show a significant interaction with IMes (**3**), while mixing benzyl mercaptan with **3** leads to rapid precipitation of imidazolium thiolate salts under conditions described in Table 2. These observations are consistent with the expected basicity of IMes.[21]

The IMes−methanol complex **8b** represents the first X-ray structure of a carbene−alcohol hydrogen-bonded complex (Figure 1).[22] The distance between the carbene C2 and the oxygen (C- -H−O) is 2.832(2) Å. The oxygen atom resides only 0.04 Å above the plane defined by the imidazolylidene-ring, thus allowing a nearly linear (174°) hydrogen bond interaction. Significantly, the N−C−N bond angle of 102.5° found in complex **8b** is much closer to the same bond angle

Table 2. Alcohol−Carbene Complexes **8a**−**d**[a]



entry	R	δ H_a (ppm)	δ H_b (ppm)	Δ (ppm)
1	**a**, ^{t}Bu	0.67	2.81	2.14
2	**b**, Me	0.05	4.37	4.32
3	**c**, $CH_2CH_2NH_2$	~0.70	5.24	~4.5
4	**d**, Bn	0.89	~6.0	~5.1

[a] ^{1}H NMR (500 MHz) data were separately recorded for the alcohols and the IMes−alcohol complexes in C_6D_6 (0.05 M) at 20 °C.

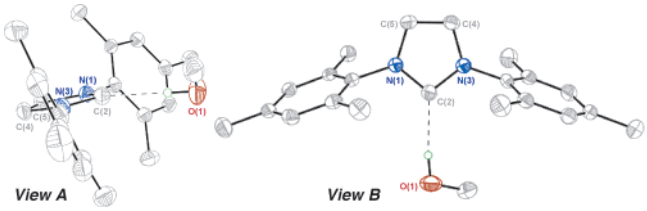


Figure 1. ORTEP drawing of complex **8b**.

(13) *N*-Fmoc-protected glycine methyl ester was found to undergo deprotection in the presence of either **3** or **2a**.

(14) See Supporting Information for details.

(15) (a) Ohta, S.; Hayakawa, S.; Okamoto, M. *Tetrahedron Lett.* **1984**, *25*, 5681−5684. (b) Davies, D. H.; Hall, J.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 837−838.

(16) Similar results were found in THF-d_8.

(17) For a review, see: Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76.

(18) For reference, the C2 and C4 resonances of carbene **3** (C_6D_6, 20 °C) are found at 219.4, and 120.9 ppm, respectively.

(19) (a) While the C2 resonance of imidazolium salts are typically >60 ppm upfield relative to the corresponding carbene C2 resonance, the reversible formation of an undetectable concentration of imidazolium alkoxide cannot be ruled out. (b) In THF-d_8, the C2 and C4 resonances of carbene **3** and complex **8b**-d_6 are found at 219.9 and 121.6 and at 212.4 and 121.6 (t, J^1_{CD} = 29.4 Hz) ppm, respectively.

(20) In the case of the more acidic alcohols, i.e., trifluoroethanol, our preliminary spectroscopic data clearly indicate a greater degree of proton transfer and the presence of multiple equilibrating complexes that include imidazolium alkoxide derivatives.

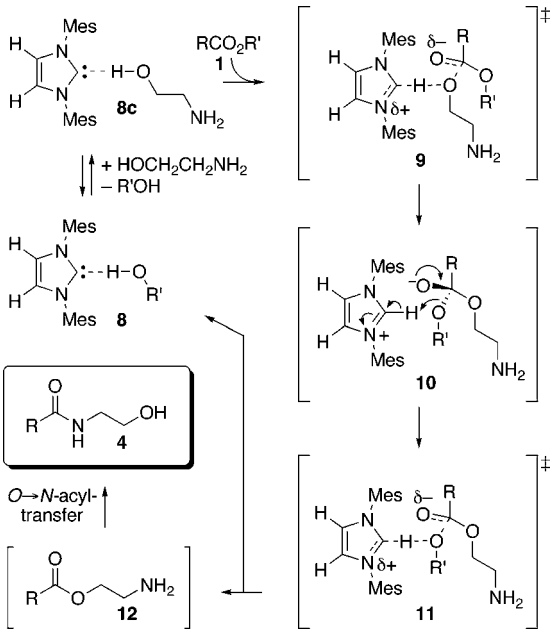
(21) (a) Arduengo, A. J., III; Gamper, S. F.; Tamm, M.; Calabrese, J. C.; Davidson, F.; Craig, H. A. *J. Am. Chem. Soc.* **1995**, *117*, 572−573. (b) Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1267−1268. (c) Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757−5761. (d) Filipponi, S.; Jones, J. N.; Johnson, J. A.; Cowley, A. H.; Grepioni, F.; Braga, D. *Chem. Commun.* **2003**, 2716−2717.

(22) For the structure of a carbene−diphenylamine complex, see: Cowan, J. A.; Clyburne, J. A. C.; Davidson, M. G.; Harris, R. L. W.; Howard, J. A. K.; Küpper, P.; Leech, M. A.; Richards, S. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1432−1434.

of 101.4° present in the parent IMes (**3**)[5b] as compared to the bond angle of 108.6° found in the corresponding bismesitylimidazolium chloride.[21a] Our results to date confirm the expectation that the degree of proton transfer in these IMes−alcohol complexes is sensitive to steric interactions, alcohol acidity, carbene basicity, and solvent. This carbene−alcohol interaction merits further consideration alongside previously reported modes of reactivity and catalysis for NHCs.

We propose a carbon-centered Brønsted base[21b] nucleophile activation for an initial transesterification followed by a rapid N→O acyl-transfer reaction (Scheme 1) to be

Scheme 1. Proposed Reaction Mechanism



operational in our chemistry. Monitoring the IMes-catalyzed coupling of γ-lactone **1m** (Table 1, entry 15, C═O, 1779 cm^{-1}) with ethanolamine (**2a**) by React-IR proceeded to give amide **4ma** (Table 1, entry 15, C═O, 1648 cm^{-1}), while a weak absorbance for a fleeting *O*-(acyl)ethanolamine ester **12ma** (Scheme 1, **12** R = $(CH_2)_3OH$, C═O, 1736 cm^{-1}) was observed during the reaction.[14] Additionally, monitoring the IMes-catalyzed amidation of methyl benzoate (**1b**) with ethanolamine (**2a**) in THF-d_8 by ^1H NMR spectroscopy clearly demonstrated the intermediacy of *O*-(benzoyl)-ethanolamine **12ba** (Scheme 1, **12** R = Ph).[14,23] Furthermore, the addition of an authentic sample of ester **12ba** (0.12 equiv) to an amidation reaction of methyl benzoate (**1b**) with ethanolamine (**2a**) in progress (at 2 h, 41% conversion) under optimal reaction conditions led to rapid O→N acyl-transfer within minutes, providing amide **4ba** (Table 1, entry 2) in 90% yield upon completion of the experiment (8 h).[14] The poor reactivity of 6-aminohexan-1-ol, 2-hydroxymethylaniline, and (2*S*,3*S*)-pseudoephedrine in coupling with methyl phenylacetate (**1a**) under our standard conditions may be due to a slow O→N acyl-transfer[24] and/or an unfavorable initial transesterification[10f] in the latter case.

The chemistry reported here provides a catalytic method for the amidation of unactivated esters with amino alcohols under mild reaction conditions with wide functional group tolerance. Our preliminary mechanistic investigations have identified a carbene−alcohol interaction that is supported by a series of solution studies in addition to the first X-ray structure of a hydrogen-bonded carbene−alcohol complex. These data taken together suggest an unexplored mode of catalysis for stable carbenes with potential mechanistic impact in other transformations. Current efforts are directed toward the development of asymmetric[25] variants of related transformations and will be reported in due time.

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Supporting Information Available: Experimental procedures and spectroscopic data for all products and crystallographic data of complex **8b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL050773Y

(23) Anhydrous lithium chloride was not used in this experiment.

(24) Kemp, D. S.; Vellaccio, F., Jr. *J. Org. Chem.* **1975**, *40*, 3464−3465.

(25) For use of NHCs in asymmetric catalysis, see refs 7d and 8e in addition to: (a) Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666−3667. (b) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876−8877. (c) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654−1655. (d) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905−908.