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Copper triflate/*t*-BuOOAc-catalyzed amidation of allylic and benzylic acetates with sulfonamides

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Abstract

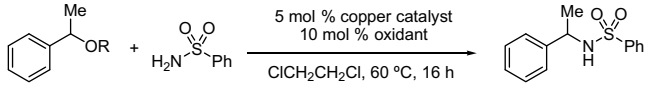
A copper triflate/*t*-BuOOAc-catalyzed amidation of allylic and benzylic acetates has been developed which is suitable for the coupling of a wide variety of functionalized sulfonamide nucleophiles with acetate electrophiles. The methodology allows for the amidation of benzylic substrates which are not further activated by an additional adjacent alkene or alkyne, enabling simple allylic acetates and primary benzylic acetates to be used as reaction partners.

Keywords: Copper; Amidation; Sulfonamide; Allylic acetate; Benzylic acetate

Methodologies which enable mild and selective C–N bond formation are of tremendous importance in organic synthesis as they facilitate the construction of complex naturally occurring and pharmacologically active molecules.[1] Advancements have led to the development of a considerable variety of methodologies for the introduction of an amine functionality; however, given the importance of this transformation, further explorations into differential methodologies will serve to supplement these existing tools.

Recently, a variety of Lewis acid[2] and Brønsted acid[3]-catalyzed methodologies for the amidation of benzylic and allylic alcohols have been disclosed.[4] Predominant among these examples are the use of benzylic alcohols which are further activated by an adjacent alkene or alkyne. In contrast, few examples of nucleophilic substitution for the synthesis of allylic or primary benzylic amides have been disclosed.[2b,c] During the course of our studies on the copper-catalyzed amidation of allylic and benzylic C–H bonds,[5] we demonstrated that a postulated benzyl acetate intermediate can be amidated with a sulfonamide under the influence of copper(II) trifluoromethanesulfonate catalyst. Herein, we disclose our explorations into the scope and utility of this transformation which proceeds with benzylic and allylic acetate substrates.[6,7]

Table 1
Reaction parameters in the copper triflate/*t*-BuOOAc-catalyzed amidation



Entry	R	Catalyst	Oxidant	Additive	Yield[a] (%)
1	Ac	None	None	None	<5
2	Ac	None	*t*-BuOOAc	None	<5
3	Ac	$Cu(OTf)_2$	None	None	35
4	Ac	$Cu(OTf)_2$	*t*-BuOOAc	None	93
5	Ac	$CuCl_2$ or $Cu(OAc)_2$	*t*-BuOOAc	None	<5
6	H	$Cu(OTf)_2$	*t*-BuOOAc	None	18[b]
7	Ac	$Cu(OTf)_2$	*t*-BuOOAc	2,6-Di-*tert*-butylpyridine (15 mol %)	<5
8	Ac	10 mol % TfOH	None	None	31
9	Ac	1 mol % TfOH	None	None	52

[a] Isolated yield after column chromatography.
[b] Determined by ^{1}H NMR analysis of the unpurified reaction mixture.

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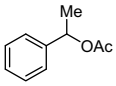
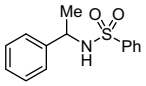
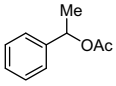
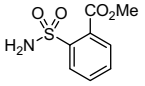
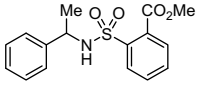
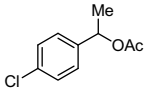
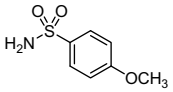
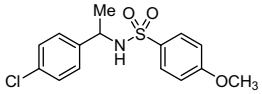
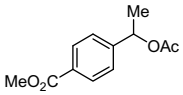
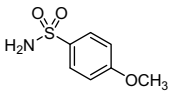
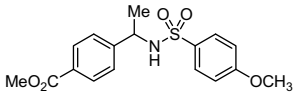
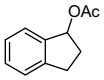
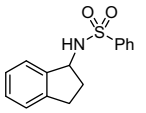
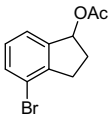
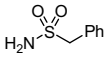
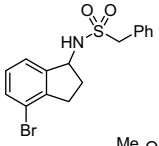
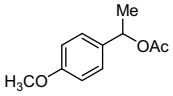
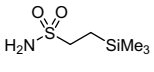
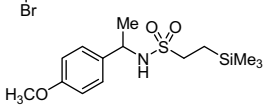
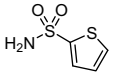
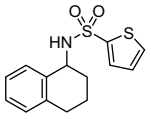
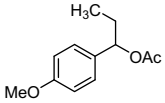
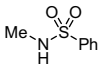
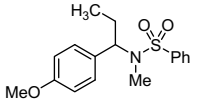
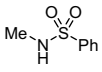
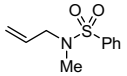
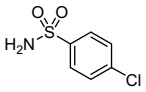
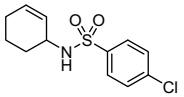
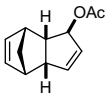
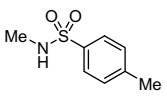
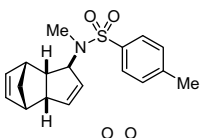
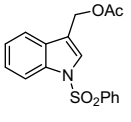
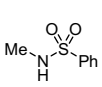
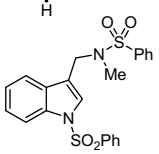
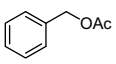
Table 2
Scope of the copper triflate/*t*-BuOOAc-catalyzed amidation of allylic and benzylic acetates with sulfonamides

Entry	Acetate	Sulfonamide	Product	Temperature (°C)	Time[a] (h)	Yield[b] (%)
1				60	6	93
2				60	6	54
3				60	6	90
4				60	16	66
5				25	6	83
6				25	16	79
7				25	6	78
8				25	16	76
9				25	6	63
10				60	16	76
11				25	16	86
12				25	1	89[c]
13				25	16	86
14				60	16	40

[a] Reaction times are not optimized.
[b] Isolated yield.
[c] A single diastereomer was isolated and the stereochemistry determined to be *exo* by ^{1}H NOE studies.

Investigation into the reaction parameters which influence the amidation protocol was explored for the representative reaction of 1-phenylethyl acetate and benzenesulfonamide (Table 1).

Critical to this transformation is the use of catalytic quantities of *both* the copper(II) trifluoromethanesulfonate (triflate) catalyst and *tert*-butylperacetate oxidant which affords the amidation product in 93% yield (entry 4). Significantly lower yields are obtained in the absence of the oxidant (entry 3), or with other copper salts (entry 5). Reaction of 1-phenylethanol under the optimized conditions yielded less than 20% of the amidation product as determined by ^{1}H NMR analysis of the unpurified reaction mixture (entry 6).

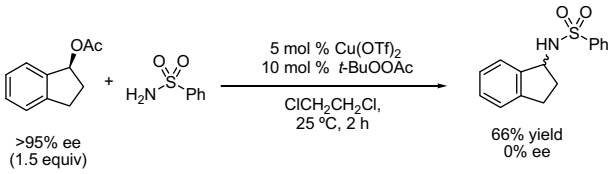
The proclivity of metal triflates to generate protic acids[8] and the previous reports on Brønsted acid-catalyzed nucleophilic substitutions of benzylic alcohols[9] prompted us to further investigate the role of the copper triflate/*t*-BuOOAc catalyst system. Importantly, in the presence of an excess of 2,6-di-*tert*-butylpyridine (15 mol %), the desired amidation product is not obtained (entry 7).[10] Amidation of the benzylic acetate does occur in the presence of triflic acid (entries 8 and 9), suggesting that Lewis acid-assisted Brønsted acid-catalysis[11] is operating in the copper triflate/*t*-BuOOAc protocol. The lower yield and concomitant formation of multiple secondary products, which interfere with product purification, demonstrate the superiority of the copper triflate/*t*-BuOOAc systems over triflic acid catalysts as a means to achieve this transformation.[12]

Having established reaction conditions for the amidation of 1-phenylethyl acetate, we then investigated the range of allylic and benzylic acetate and sulfonamide coupling partners which could be employed (Table 2). Most reactions occur at room temperature, although some allylic and benzylic acetates require heating to 60 °C to achieve full conversion. Arylsulfonamides with either electron-withdrawing or electron-donating substituents serve as suitable reaction components (entries 2 and 3), although lower yields are observed with the more electron-deficient sulfonamides.[13]

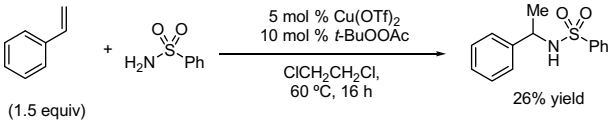
In addition to arylsulfonamides, 2° sulfonamides (entries 9 and 10, 12–14), heteroarylsulfonamides (entry 8) and alkylsulfonamides (entries 6 and 7) can be utilized, including the readily cleaved trimethylsilylethylsulfonamide[14] (entry 7). The more sterically hindered 1-arylphenylpropyl acetate (entry 9) and the primary indole methyl acetate (entry 13) underwent facile amidation at room temperature. Notably, this methodology is also suitable for the amidation of allylic acetates (entries 10–12), including the tricyclic deca-4,8-dien-3-yl acetate (entry 12), which afforded the amidation product as a single diastereomer.

The reaction has been conducted on a 10-fold larger scale without compromising either the yield or the operational simplicity of the procedure. Reaction of 1-phenylethyl acetate and benzenesulfonamide on a 30 mmol scale afforded the amidation product in 89% yield (6.94 g) compared to 93% when conducted on a 3 mmol scale (Table 2, entry 1).

To gain further insight into the mechanism of this transformation, we explored the reaction of a chiral benzylic acetate (Eq. 1) under the copper triflate/*t*-BuOOAc catalyst system. Amidation under standard conditions resulted in a the formation of a racemic product, consistent with a benzylic cation intermediate.[15]



(1)



(2)

In the related reactions of benzylic alcohols, symmetrical ethers (e.g., bis(1-phenylethyl) ether) have been observed as intermediates.[2g,4a] Similar products have not been detected in our copper triflate/*t*-BuOOAc-catalyzed amidation procedure; however, we have observed small amounts of styrene derivatives in the crude reaction mixture, resulting from the elimination of acetic acid from the benzylic acetate electrophile.

To investigate the possibility of whether an elimination–hydroamidation mechanism was operating,[16] we explored the reaction of styrene with benzenesulfonamide under the copper triflate/*t*-BuOOAc catalysts system. This afforded the amidation product in significantly lower yield (Eq. 2). While the lower yield of the amidation product obtained with styrene versus 1-phenylethyl acetate does not exclude a mechanism whereby amidation proceeds via acetic acid elimination followed by hydroamidation, we propose that the reaction more likely proceeds via a direct trapping of an allylic or benzylic cation with the sulfonamide nucleophile.[17]

In summary, we have developed a copper triflate/*t*-BuOOAc-catalyzed amidation of allylic and benzylic acetates which is suitable with a wide variety of functionalized sulfonamide nucleophiles and acetate electrophiles. The methodology allows for the amidation of benzylic substrates which are not further activated by an additional adjacent alkene or alkyne, enabling simple allylic acetates and primary benzylic acetates to be used as substrates.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.135.

References and notes

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12. It is unclear at this point why the copper triflate/*t*-BuOOAc-catalyzed system gives higher yields than triflic acid alone. An oxidized copper triflate-complex may be playing a role in buffering the available concentration of triflic acid. It is known that larger concentrations of Brønsted acids have a detrimental effect on similar reactions, see Ref. 8a.
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