Sp–sp^3 C–C bond formation *via* Fe(OTf)$_3$/TfOH cocatalyzed coupling reaction of terminal alkynes with benzylic alcohols†

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An Fe(OTf)$_3$/TfOH cocatalyzed sp–sp^3 C–C bond formation through the coupling of benzylic alcohols with terminal alkynes in the absence of base has been developed. H_2O is the sole by-product.

The development of new methods for introducing an alkyne unit into organic molecules is one of the most exciting topics in practical organic synthesis, because alkynes are widely distributed in a vast array of natural products, bioactive compounds and drugs,[1] as well as being ubiquitous units in material science.[2] During the past several decades, the palladium- and/or copper-catalyzed Sonogashira cross-coupling reactions[3] of terminal alkynes with aryl or alkenyl halides have been among the most powerful methods available for the formation of sp–sp^2 C–C bonds (eqn (1)). However, sp–sp^3 C–C bond formation *via* the coupling of terminal alkynes with alkyl electrophiles has been less widely explored.[4] Recently, Eckhardt and Fu achieved the Sonogashira coupling of primary alkyl halides.[5a] Efficient protocols for the alkynylation of benzyl[5b] or secondary alkyl halides[5c] were also realized by Buchwald's and Glorius' groups, respectively.[6] However, alkyl halides were required and halide byproducts were produced by these methods. Alternatively, if an alcohol could be employed as the alkyl electrophile, H_2O would be the sole by-product, making the transformation atom efficient and environmentally benign (eqn (2)). Herein, we report an Fe(OTf)$_3$/TfOH cocatalyzed coupling reaction of terminal alkynes with benzylic alcohols in the absence of base leading to sp–sp^3 C–C bond formation.

$$\mathrm{R{-}X} + \mathrm{H{-}{\equiv}{-}R'} \xrightarrow[\text{base}]{\text{Pd catalyst}\atop\text{Cu catalyst}} \mathrm{R{-}{\equiv}{-}R'} \qquad (1)$$

$$\mathrm{R{-}OH} + \mathrm{H{-}{\equiv}{-}R'} \xrightarrow[\text{-}H_2O]{\text{catalyst}} \mathrm{R{-}{\equiv}{-}R'} \qquad (2)$$

Compared to alkyl halides or esters, the corresponding alcohols do not easily react with nucleophiles due to the poor hydroxyl leaving group. Nonetheless, alcohols are plentiful and inexpensive. In addition, the direct coupling reaction of alcohols is environmentally benign, generating H_2O as the side product. Hence, the carbon–carbon bond formation using an alcohol as a substrate has attracted great interest from organic chemists.[7] Recently, Kabalka and co-workers realized the substitution of hydroxyl groups with alkynylboron dihalides.[8] However, the use of alkynylboron dihalides as nucleophiles and the requirement of 2 equiv. of n-BuLi limits its application.

Lately, iron catalysts[9,10] have been extensively investigated and it has been reported that alcohols are easily activated by them.[7a,g,h,n] Moreover, the reaction of terminal alkynes can also be facilitated by iron catalysts.[11] We envisioned that the coupling reaction between terminal alkynes and alcohols catalyzed by an iron salt would be feasible.

Initially, we investigated the reaction of benzhydrol **1a** and phenylacetylene **2a** in the presence of 5 mol% of Fe(OTf)$_3$. Gratifyingly, 61% of **3aa** was obtained when dichloroethane (DCE) was used as the solvent (entry 2, Table 1). Although various Lewis acids such as In(OTf)$_3$, AgOTf and Cu(OTf)$_2$ can perform this transformation, their efficiencies were lower than that of Fe(OTf)$_3$ (see ESI†). Notably, TfOH[12] can also catalyze this reaction giving **3aa** in 57% yield (entry 3, Table 1). However, the relatively weak acid TsOH hardly led to any of the desired product (entry 4, Table 1). In particular, this reaction was strongly influenced by the solvents. Polar solvents (DMF and $MeNO_2$) were not suitable for this transformation (entries 5–6). After a great deal of screening on different parameters, the highest yield (77%) was reached cocatalyzed by Fe(OTf)$_3$ (5 mol%) and TfOH (10 mol%) in DCE (entry 7, Table 1). The collaboration of Fe(OTf)$_3$ and TfOH presents positive effect on the transformation compared to the corresponding individual employment of these catalysts (*cf.* entry 7 with entries 10 and 12, Table 1). To the best of our knowledge, this is the first Fe(OTf)$_3$ and TfOH cooperative catalysis.[13] Markedly, even when 2 mol% of Fe(OTf)$_3$ and 5 mol% of TfOH were employed, the coupling went well giving 70% yield (entry 9, Table 1).

The scope of this Fe(OTf)$_3$/TfOH cocatalyzed coupling reaction was expanded to a variety of substituted benzylic alcohols (Table 2). Benzylic alcohols with electron-donating groups smoothly underwent this kind of transformation, generating **3** in moderate to excellent yields (54–86%). Chloro-substituted benzylic alcohol **1f** survived well, leading to **3fa** in 66% yield (entry 6). Notably, all *para*-, *meta*-, and *ortho*-substituted benzylic alcohols could be smoothly transformed into the desired products (entries 2–4, Table 2).

To investigate the scope of the terminal alkynes in this transformation, benzhydrol **1a** was chosen as the substrate to react with different terminal alkynes. The results in Table 3 show that both electron-rich and electron-deficient

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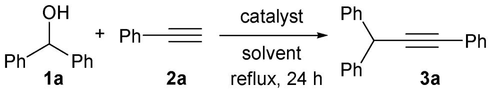
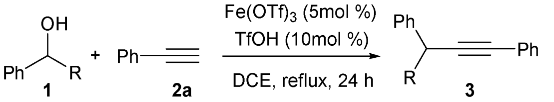
Table 1 The coupling reaction of benzhydrol **1a** with phenylacetylene **2a** under different conditions[a]



Entry	Catalyst (mol%)	Solvent	Yield of **3aa** (%)[b]
1	—	DCE	0
2	Fe(OTf)$_3$ (5)	DCE	61
3	TfOH (5)	DCE	57
4	TsOH (5)	DCE	Trace
5[c]	Fe(OTf)$_3$ (5)	DMF	Trace
6[c]	Fe(OTf)$_3$ (5)	MeNO$_2$	Trace
7	**Fe(OTf)$_3$ (5)/TfOH (10)**	**DCE**	**77**
8	Fe(OTf)$_3$ (5)/TsOH (10)	DCE	59
9	Fe(OTf)$_3$ (2)/TfOH (5)	DCE	70
10	Fe(OTf)$_3$ (15)	DCE	63
11	TfOH (10)	DCE	64
12	TfOH (15)	DCE	63
13[d]	Fe(OTf)$_3$ (5)/TfOH (10)	DCE	18

[a] All the reactions were carried out on the scale of 0.5 mmol of **1a** with 0.75 mmol of **2a**, catalyst, and 2 ml solvent under N$_2$. The TfOH was a 2 M solution in DMF. [b] Isolated yields. [c] The reaction was carried out at 90 °C. [d] The reaction was carried out at 70 °C.

Table 2 Fe(OTf)$_3$ and TfOH cocatalyzed coupling reaction of benzylic alcohols **1** with phenylacetylene **2a**[a]



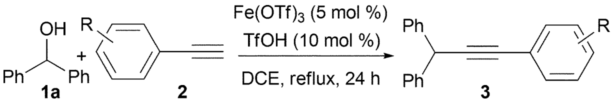
Entry	R (**1**)		Yield of **3** (%)[b]	
1	Ph	**(1a)**	77	**(3aa)**
2	*o*-Me-C$_6$H$_4$–	**(1b)**	86	**(3ba)**
3	*m*-Me-C$_6$H$_4$–	**(1c)**	62	**(3ca)**
4	*p*-Me-C$_6$H$_4$–	**(1d)**	72	**(3da)**
5	*p*-MeO-C$_6$H$_4$–	**(1e)**	54	**(3ea)**
6	*p*-Cl-C$_6$H$_4$–	**(1f)**	66	**(3fa)**
7	*p*-Ph-C$_6$H$_4$–	**(1g)**	77	**(3ga)**
8	*p*-^{t}Bu-C$_6$H$_4$–	**(1h)**	72	**(3ha)**

[a] All the reactions were carried out on the scale of 0.5 mmol of **1** with 0.75 mmol of **2a**, 0.025 mmol Fe(OTf)$_3$, 0.05 mmol TfOH (2 M in DMF), and 2 ml solvent under N$_2$. [b] Isolated yields.

arylacetylenes were tolerable as the coupling partners. Bromo-substituted phenylacetylene **2e** was successfully converted to bromo-substituted product **3ae** in 79% yield (entry 5, Table 3), which could be used for further transformations. Moreover, with a methyl substituent at the *meta*- or *ortho*-positions (**2c**, **2d**) a higher yield was obtained than with a methyl substituent at the *para*-position (**2b**) (entries 2–4, Table 3).

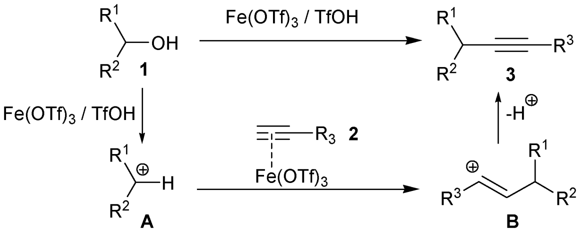
Based on the above results, a plausible mechanism is proposed in Scheme 1. Benzylic alcohols **1** are initially activated by Fe(OTf)$_3$ and TfOH, generating the cationic intermediates **A**.[7h] Then, the intermolecular addition with terminal alkynes **2** activated by Fe(OTf)$_3$ would proceed to give intermediates **B**,[7h,14] followed by deprotonation to form the corresponding products **3**.[7i]

Table 3 Fe(OTf)$_3$ and TfOH cocatalyzed coupling reaction of benzhydrol (**1a**) with different alkynes **2**[a]



Entry	R (**2**)		Yield of **3** (%)[b]	
1	H	**(2a)**	77	**(3aa)**
2	*p*-Me	**(2b)**	56	**(3ab)**
3	*o*-Me	**(2c)**	81	**(3ac)**
4	*m*-Me	**(2d)**	75	**(3ad)**
5	*p*-Br	**(2e)**	79	**(3ae)**
6	*p*-F	**(2f)**	80	**(3af)**
7	*p*-Ph	**(2g)**	63	**(3ag)**

[a] All the reactions were carried out in the scale of 0.5 mmol of **1a** with 0.75 mmol of **2**, 0.025mmol Fe(OTf)$_3$, 0.05 mmol TfOH (2 M in DMF), and 2 ml solvent under N$_2$. [b] Isolated yields.



Scheme 1 Proposed mechanism of the coupling between terminal alkynes and benzylic alcohols cocatalyzed by Fe(OTf)$_3$ and TfOH.

In summary, we developed a Fe(OTf)$_3$/TfOH cocatalyzed coupling reaction of benzylic alcohols with terminal alkynes resulting in the sp–sp^3 C–C bond formation in the absence of base. Inexpensive iron and TfOH are used as catalysts. Furthermore, H$_2$O is the unique byproduct makes this transformation atom efficient and environmentally benign. This method presents a novel example of efficient cooperative catalysis. Further studies on the scope and the synthetic applications are ongoing in our laboratory.

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