Catalytic direct-type substitution reaction of α-alkyl enolates: a Pd/Brønsted base-catalysed approach to the decarboxylative allylation of sulfonylimidates†‡

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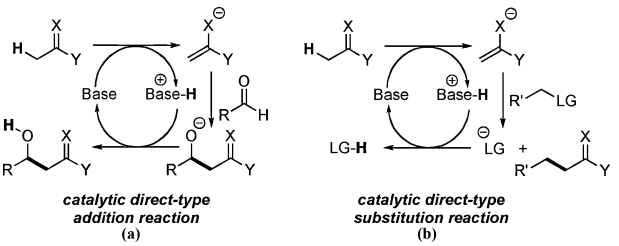
A mild and efficient process for the direct-type catalytic allylation of sulfonylimidates has been developed; this reaction represents the first example of Brønsted base-catalysed, *in situ* generation and use of α-alkyl enolates in substitution reactions; the success of this methodology stems from the tunable α-proton acidity and nucleophilicity of sulfonylimidates, which could be harnessed in the realization of a broader range of catalytic direct-type reactions using ester equivalents as nucleophiles.

In response to the limited precedence for the use of α-alkyl esters in catalytic direct-type reactions, our laboratory has become interested in designing suitable nucleophiles and reaction systems for the realization of this goal.[1] Compared with activated ester nucleophiles, such as those bearing a π system or heteroatom adjacent to the ester functionality, the α-proton pK_a value of simple α-alkyl esters is markedly higher and renders *in situ* catalytic enolate formation a formidable challenge. Recently, we and others have proposed solutions to this problem in the context of catalytic carbonyl and Michael-type addition reactions, through the use of α-alkyl ester equivalents, including sulfonylimidates,[1a] (*N*-Boc)anisidides,[1b,c] and trichloromethyl ketones[2] as nucleophiles. Appropriate catalytic systems were designed to complement these substrates, such that a metal complex or simply a tertiary amine could be used to promote proton transfer from the carbonyl nucleophile to the addition adduct, and thereby effect carbon–carbon bond formation under complete catalytic conditions (Scheme 1a).

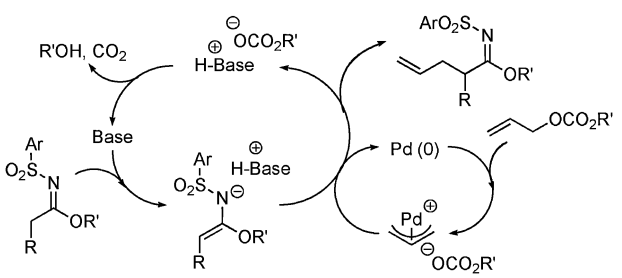
Catalytic direct-type *substitution* reaction of α-alkyl esters/ester equivalents, on the other hand, has not been realized to date.[3] Our strategy to implement this type of reaction is to use the leaving group to serve as a proton sink in the catalytic system. For this purpose, the leaving group would, despite its good leaving group ability, need to be sufficiently basic. We anticipated that a carbonate functionality would be suitable in this regard, which upon nucleophilic substitution and subsequent decarboxylation would generate an alkoxide anion appropriate for Brønsted base regeneration (Scheme 1b). External base-free, palladium-catalysed decarboxylative



Scheme 1 Catalytic direct-type (a) addition and (b) substitution reactions (X, Y = heteroatoms).

substitution is a well studied process for the functionalization of carbonyl compounds such as malonates and β-ketoesters.[4] For simple esters, however, the propensity of deprotonation is inadequate to promote the reaction under neutral conditions. In order to overcome this limitation, we proposed to introduce a *catalytic* amount of external base to the system, and to activate the carbonyl α-proton by electronic modification at the nucleophile. These considerations, coupled with our recent efforts to develop nitrogen analogues of carboxylic ester as readily tunable nucleophiles, led us to investigate the substitution of allyl carbonates by sulfonylimidates. Our choice of sulfonylimidates resides also on the ease to transform this functionality[1a] to the corresponding amide, ester[5] and aldehyde, and their applications in medicinal chemistry.[6] Our conceptual design is depicted in Scheme 2.

Initial experiments showed that this strategy was feasible. A combination of Pd(0) catalyst (10 mol%) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 20 mol%) effected the direct allylation with good yield and regioselectivity upon heating in toluene (Scheme 3). Importantly, double allylation or tautomerisation of the mono-allylated product to the corresponding enesulfonamide was not observed. The reaction did not proceed in the absence of an external base, or when a weaker amine base (Et_3N) was used. Conducting the reaction



Scheme 2 Proposed Pd and Brønsted base-cocatalysed decarboxylative allylation of sulfonylimidate.

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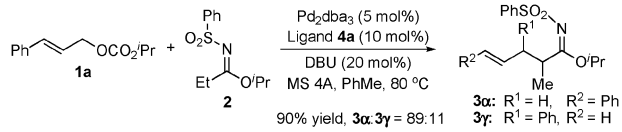
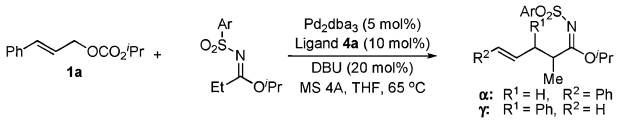


Scheme 3 Pd and DBU-catalysed allylation of sulfonylimidate with cinnamyl carbonate.

Table 1 Electronic effect of sulfonylimidate in decarboxylative allylation reaction



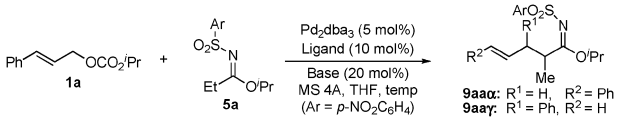
Entry	Ar	Time/h	Yield (%)	α : γ
1	*p*-$NO_2C_6H_4$ (**5a**)	4	73	93 : 7
2	*p*-$CF_3C_6H_4$ (**6**)	3	<31[a]	—[b]
3	*m*-$CF_3C_6H_4$ (**7**)	3	<24[a]	—[b]
4	Ph (**8**)	48	89	94 : 6
5	*p*-$MeOC_6H_4$ (**8**)	10	88	92 : 8

[a] Conversion. [b] Not determined.

in refluxing THF improved the regioselectivity (**3α** : **3γ** = 94 : 6, 89% yield), but an attempt to reduce the reaction temperature further led to a marked decrease in reactivity.

We reasoned that the relatively poor reactivity observed might stem from the difficulty in generating an α-alkyl enolate by catalytic deprotonation and the low concentration of such an intermediate. The use of inorganic bases was thought to stabilize the imidate enolate and improve reactivity *via* metal enolate formation, but this approach was unsuccessful and no inorganic base examined was found to be compatible with our reaction system.[7] Another solution to this problem would be to modify the imidate sulfonyl-substituent and accordingly, "tune" the α-proton acidity, enolate stability and nucleophilicity

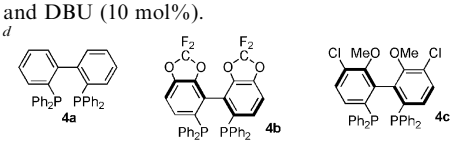
Table 2 Pd and amine base-catalysed allylation of sulfonylimidate with cinnamyl carbonate



Entry	Ligand[d]	Base	Temp/°C	Yield (%)[a]	**9aaα** : **9aaγ**[b]
1	**4a**	DBU	65	73	93 : 7
2	**4a**	Et_3N	65	94	94 : 6
3	**4a**	DBU	rt	59	96 : 4
4	**4b**	DBU	rt	75	91 : 9
5	**4c**	DBU	rt	79	95 : 5
6[c]	**4c**	DBU	rt	83	95 : 5

[a] Isolated yield. [b] Determined by ^{1}H NMR of crude products. [c] The reaction was performed using Pd_2dba_3 (2.5 mol%), ligand **4c** (5 mol%) and DBU (10 mol%).

[d]

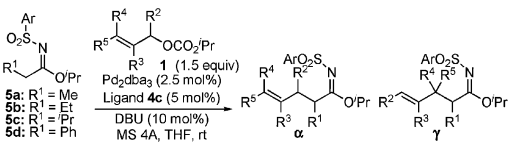


of sulfonylimidate. Gratifyingly, when a *para*-nitrobenzene ring was incorporated, which we believed should lower the α-proton pK_a value and stabilize the aza-enolate by an inductive effect, remarkable rate acceleration was observed (Table 1). On the other hand, the introduction of less electron-withdrawing substituents (**6** and **7**) was not as effective. Interestingly, the use of electron-rich imidate **8** also led to rapid allylation, presumably fast nucleophilic attack could sufficiently drive the equilibrium to favour enolate formation.

Armed with this information, we chose *N*-(*p*-nitrobenzenesulfonyl)imidate **5a** to further improve our reaction system. A weaker base, such as Et_3N, also catalysed the reaction with excellent yield and selectivity (Table 2, entry 2). Efficient allylation was possible at room temperature using a somewhat electron-deficient ligand,[8] and the catalyst loading could be reduced to 2.5 mol% Pd_2dba_3 and 10 mol% DBU (Table 2, entry 6).

We next investigated the substrate scope of this reaction (Table 3). Various substitutions in the α-position of sulfonylimidate could be accommodated: methyl, ethyl, and the sterically more demanding isopropyl group all gave comparable results with excellent yields. Allylation of stabilized α-aryl sulfonylimidate **5d** was hampered by a competing *N*-allylation pathway, which was found to be irreversible under the reaction conditions (entries 1–4). Linear aromatic, heteroaromatic and aliphatic allyl carbonates with either *E* or *Z* olefin geometry

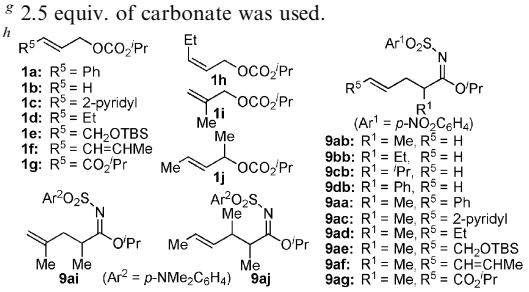
Table 3 Catalytic direct-type allylation of sulfonylimidates (Ar = *p*-$NO_2C_6H_4$)



Entry	Imidate	Carbonate[h]	α-Adduct[h]	Yield (%)[a]	α : γ[b]
1	**5a**	**1b**	**9ab**	99	—
2	**5b**	**1b**	**9bb**	99	—
3	**5c**	**1b**	**9cb**	95	—
4	**5d**	**1b**	**9db**	74	—
5	**5a**	**1a**	**9aa**	83	95 : 5
6	**5a**	**1c**	**9ac**	82	91 : 9
7[c]	**5a**	**1d**	**9ab**	72	96 : 4
8[c]	**5a**	**1h**	**9ad**	70	94 : 6
9[c]	**5a**	**1e**	**9ae**	87	97 : 3
10[d]	**5a**	**1i**	**9ai**	99	—
11[d]	**5a**	**1j**	**9aj**	73	—[e]
12[f]	**5a**	**1f**	**9af**	93	69 : 31
13[g]	**5a**	**1g**	**9ag**	98	99 : 1

[a] Isolated yield. [b] Determined by ^{1}H NMR of crude products. [c] At 30 °C. [d] Ar = *p*-$NMe_2C_6H_4$, at 65 °C. [e] dr = 70 : 30. [f] At 0 °C. [g] 2.5 equiv. of carbonate was used.

[h]



gave *E*-products exclusively with excellent regioselectivity (entries 5–9). Branched and 1,3-disubstituted allyl carbonates were found to be less reactive substrates, but the desired products could be obtained in good to excellent yields when an electron-rich sulfonylimidate was employed (entries 10–11). Sensitive γ-diene functionality could be incorporated into the allylation product, albeit in moderate regioselectivity (entry 12). The reaction conditions also accommodated the use of a bifunctional electrophile and provided the desired α-allylation product in a complete chemo- and regioselective manner (entry 13).

In summary, we have demonstrated a palladium/Brønsted base-catalysed strategy to the decarboxylative allylation of nitrogen analogues of carboxylic ester. This approach effected carbon–carbon bond-forming substitution reactions under mild and complete catalytic conditions, which would be appealing for large scale syntheses and the preparation of molecules that bear base-sensitive functionality or stereochemistry. This report represents the first direct catalytic substitution reaction of α-alkyl ester equivalents, the underlying concept of which could be extended to other substitution reactions. Further studies in developing asymmetric versions of this reaction, as well as expanding the scope of using transition metal and Brønsted base as cocatalysts and the utility of sulfonylimidates as nucleophiles are now underway in our laboratory.

Notes and references

1 (*a*) R. Matsubara, F. Berthiol and S. Kobayashi, *J. Am. Chem. Soc.*, 2008, **130**, 1804; (*b*) S. Saito and S. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 8704; (*c*) S. Saito, T. Tsubogo and S. Kobayashi, *Chem. Commun.*, 2007, 1236.

2 (*a*) H. Morimoto, S. H. Wiedemann, A. Yamaguchi, S. Harada, Z. Chen, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2006, **45**, 3146; (*b*) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 9588.

3 Recently, an example of palladium-catalysed allylation of α-alkyl amides using a *stoichiometric* amount of strong base was reported, see: K. Zhang, Q. Peng, X.-L. Hou and Y.-D. Wu, *Angew. Chem., Int. Ed.*, 2008, **47**, 1741.

4 For pioneering work of the use of allyl carbonates in palladium-catalysed allylation under neutral conditions, see: (*a*) J. Tsuji, I. Shimizu, I. Minami and Y. Ohashi, *Tetrahedron Lett.*, 1982, **23**, 4809; (*b*) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura and K. Takahashi, *J. Org. Chem.*, 1985, **50**, 1523; For a general review of the Tsuji–Trost reaction, see: (*c*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (*d*) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258, and references cited therein.

5 An additional protocol for the conversion of sulfonylimidates to the corresponding esters under mild hydrolysis conditions has been developed in this work, see ESI‡ for details.

6 Sulfonylimidates as prodrug candidates: (*a*) H. Bundgaard and J. D. Larsen, *J. Med. Chem.*, 1988, **31**, 2069; (*b*) J. D. Larsen and H. Bundgaard, *Int. J. Pharm.*, 1989, **51**, 27.

7 The inorganic bases examined included NaO^tBu, LiO^tBu, $Mg(O^tBu)_2$ and Cs_2CO_3.

8 The non-racemic version of this ligand gave only low enantioselectivity (see ESI†).