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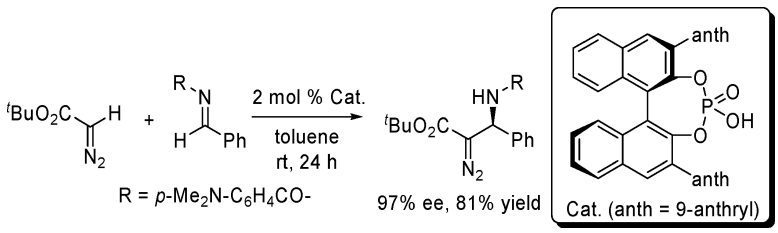


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# Organocatalytic Asymmetric Direct Alkylation of α-Diazoester via C−H Bond Cleavage

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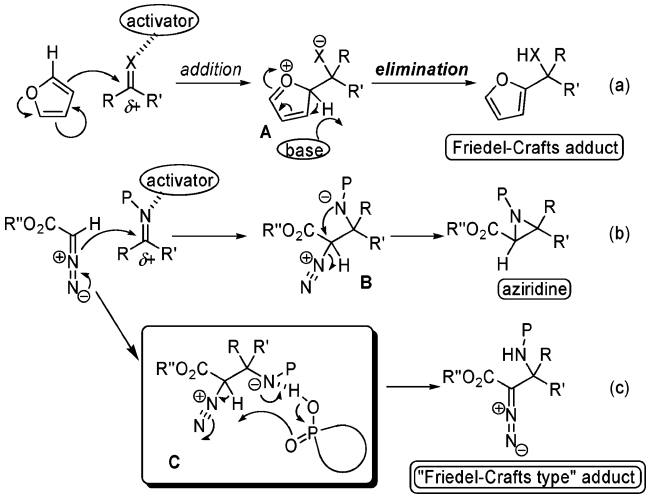
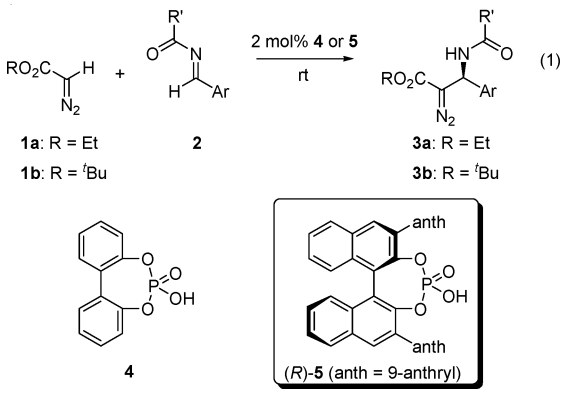
The catalytic asymmetric $sp^2$ C−H bond addition reaction to carbonyl, imine, and α,β-unsaturated carbonyl compounds, such as Friedel−Crafts (F−C) alkylations, is a powerful yet challenging organic transformation.[1] It has attracted much attention from industry as well as the academic community due to its atom efficiency.[2] Recently, highly enantioselective 1,2- and 1,4-F−C alkylations were achieved using metal-based Lewis acid[3] and small organomolecule[4,5] catalysts. Mechanistically, these F−C alkylations are regarded to proceed via an addition−elimination pathway (Scheme 1a). For instance, an electron-rich aromatic or heteroaromatic compound attacks an activated $sp^2$ carbon, and subsequent deprotonation provides an F−C alkylation product exclusively.

***Scheme 1.*** Mechanism for Friedel−Crafts Alkylations and Reaction Modes of Diazoacetate with Imine




In conjunction with our recent efforts to develop chiral Brønsted acids for catalyzed asymmetric carbon−carbon bond forming reactions,[6−9] we recently demonstrated a highly enantioselective 1,2-aza-F−C reaction of a furan derivative to *N*-protected aldimines catalyzed by chiral phosphoric acid.[9] In consideration of the catalytic cycle of this reaction, the phosphate anion receives a proton in the elimination stage, and it is even possible that the phosphoryl oxygen functions as an intracomplex basic site. Diazoacetate, which has an electronically unique $sp^2$ carbon, is a rather interesting motif from this viewpoint because of the similarity of the addition intermediates **A** and **B**. Although diazoacetate is commonly used in aziridine formation reactions (aza-Darzens reaction) under Lewis[10] and Brønsted[11] acidic conditions (Scheme 1b), a possible intracomplex deprotonation from intermediate **C** by phosphoryl oxygen may allow direct alkylation of diazoacetate via C−H bond cleavage, giving an α-diazo-β-amino acid ester through an "F−C-type" pathway (Scheme 1c). Thus, treatment of ethyl diazoacetate (**1a**) with an acyl imine (**2**, R′, Ar = Ph) was attempted at room temperature in chloroform-d1 under the influence of 2 mol % of achiral phosphoric acid (**4**, eq 1). As desired, clean conversion of the starting imine (**2**, R′, Ar = Ph) to the direct alkylation product (**3a**, R′, Ar = Ph) was observed within 1 h, and the product was isolated in 70% yield. Although it is difficult to clarify the action of the phosphoryl oxygen work in the deprotonation stage, this result indicates that a phosphoric acid catalyst such as **4** can efficiently promote direct alkylation of α-diazoesters via C−H bond cleavage.[12] Herein, we describe development of the asymmetric form by means of a binaphthol monophosphoric acid catalyst.[13]




Catalyst (*R*)-**5**[14] provided the best enantioselectivity of the reactions attempted, and its selectivity was dramatically influenced by tuning of the ester moiety of **1**. For example, the 79% ee obtained for the ethyl ester was ameliorated to 84% ee when using isopropyl ester in toluene at room temperature and was further improved to 90% ee using commercially available *tert*-butyl diazoacetate (**1b**) as a substrate. Interestingly, the electronic character of the acyl protective group of the imine nitrogen also strongly affected selectivity as well as reactivity (Table 1). Introduction of ortho- or meta-substituents to the acyl aromatic moiety indicated a small effect on the selectivity (entries 1−6). However, para-substituents strongly impacted on the reaction selectivity as well as frequency and introduction of electron-donating substituents provided better results (entries 7−9). The highest selectivity was displayed by *para*-dimethylaminobenzoyl aldimine (**2**, R′ = *p*-$Me_2N-C_6H_4$, Ar = Ph) although with a slight reduction in reaction frequency (entry 10). Fortunately, a prolonged reaction time improved the yield (entry 11).

Experiments that probe the scope of this transformation are summarized in Table 2. Para-substituted aromatics showed generally excellent enantioselectivity irrespective of its electronic character (entries 1−4). Ortho- and meta-substitution as well as a fused ring system was also tolerated (entries 5−8).

Next, we attempted to derive the common synthetic intermediates, β-amino acid derivatives, from **3b**. Hydrogenation of the diazo

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***Table 1.*** Electronic Effect of Acyl Protective Group on the Imine Nitrogen (Eq 1, Ar = Ph, **1b**, and (*R*)-**5** Were Used)[a]

| entry | R′ | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | Ph | 59 | 90 |
| 2 | *o*-Br−$C_6H_4$− | 80 | 90 |
| 3 | *o*-Me-$C_6H_4$− | 84 | 90 |
| 4 | *o*-MeO−$C_6H_4$− | 77 | 92 |
| 5 | *m*-MeO−$C_6H_4$− | 76 | 91 |
| 6 | 1-naphthyl− | 82 | 90 |
| 7 | *p*-Br−$C_6H_4$− | 68 | 86 |
| 8 | *p*-Me-$C_6H_4$− | 72 | 91 |
| 9 | *p*-MeO−$C_6H_4$− | 73 | 93 |
| 10 | *p*-$Me_2N$−$C_6H_4$− | 57 | 96 |
| 11[d] | *p*-$Me_2N$−$C_6H_4$− | 81 | 97 |

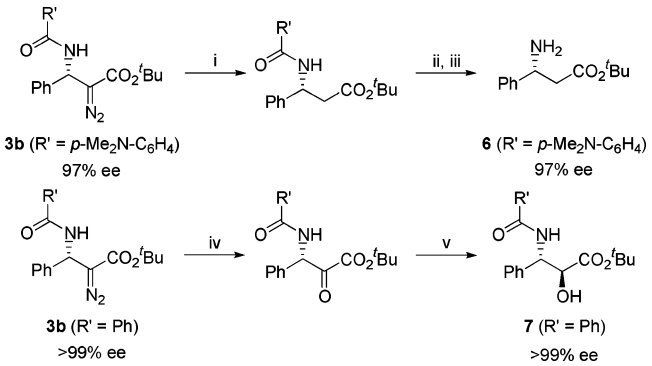
[a] Unless otherwise noted, all reactions were carried out with 0.1 mmol of **1** in 1 mL of toluene at room temperature for 5 h. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis. See Supporting Information for details. [d] The reaction was carried out for 24 h.

***Table 2.*** Organocatalyzed Direct Alkylation of *tert*-Butyl Diazoacetate (**1b**) with Representative Aldimine Derivatives (**2**) (Eq 1, R′ = *p*-$Me_2N$-$C_6H_4$, **1b**, and (*R*)-**5** Were Used)[a]

| entry | Ar | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | *p*-F-$C_6H_4$- | 74 | 97 |
| 2 | *p*-Ph-$C_6H_4$- | 71 | 97 |
| 3 | *p*-Me-$C_6H_4$- | 74 | 97 |
| 4 | *p*-MeO-$C_6H_4$- | 62 | 97 |
| 5[d] | *o*-F-$C_6H_4$- | 89 | 91 |
| 6 | *o*-MeO-$C_6H_4$- | 85 | 91 |
| 7 | *m*-F-$C_6H_4$- | 84 | 93 |
| 8[d] |  | 75 | 95 |

[a] All reactions were carried out with 0.1 mmol of **1** in 1 mL of toluene at room temperature for 24 h. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis. See Supporting Information for details. [d] 3 mol % of (*R*)-**5** was used.

***Scheme 2.*** Synthetic Utility of β-Amino-α-Diazoesters[a]




[a] Conditions: (i) $PtO_2$, $H_2$, EtOAc/AcOH, room temperature (rt), 79%. (ii) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78 to 0 °C, then MeOH, 0 °C to rt, 70%. (iii) Pd/C, $H_2$, MeOH, rt, 60%. (iv) Oxone, $NaHCO_3$, $H_2O$/acetone/$CH_2Cl_2$, 0 °C to rt. (v) $NaBH_4$, MeOH, −78 °C, anti/syn = >99:<1, 95% (in two steps).

moiety of **3b** (R′ = *p*-$Me_2N$−$C_6H_4$, Ar = Ph, 97% ee) with Adams' catalyst under a hydrogen atmosphere and successive deprotection provided β-amino acid *tert*-butylester (**6**) without any loss of enantiomeric excess. α-Oxo-functionality was efficiently introduced by oxone, and subsequent diastereoselective reduction enabled us to synthesize *anti*-β-amino-α-hydroxy acid *tert*-butylester (**7**) from **3b** (R′, Ar = Ph, recrystallized, >99% ee).[15] These short step syntheses of β-amino acid derivatives with high optical purity by means of functionalization of diazo moiety clearly highlight the diverse synthetic potential of this direct asymmetric transformation.

In conclusion, a new variant of phosphoric acid-catalyzed C−C bond forming reaction, direct alkylation of α-diazoester, via C−H bond cleavage was presented. The resulting products, β-amino-α-diazoesters, are highly functionalized and useful synthetic precursors for various types of β-amino acids. Further synthetically useful direct transformations promoted by chiral phosphoric acid catalysts are underway.

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**Supporting Information Available:** Representative experimental procedures and spectroscopic data for **2**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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