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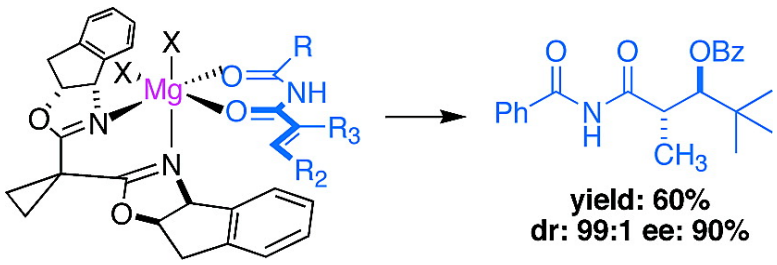

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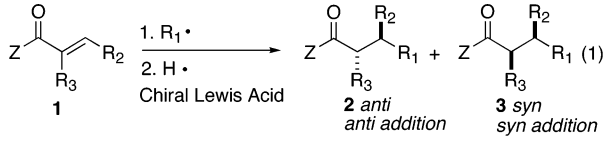
Enantioselective Radical Addition/Trapping Reactions with α,β-Disubstituted Unsaturated Imides. Synthesis of *anti*-Propionate Aldols

Mukund P. Sibi,* Goran Petrovic, and Jake Zimmerman

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105.

Received November 2, 2004; E-mail: mukund.sibi@ndsu.edu

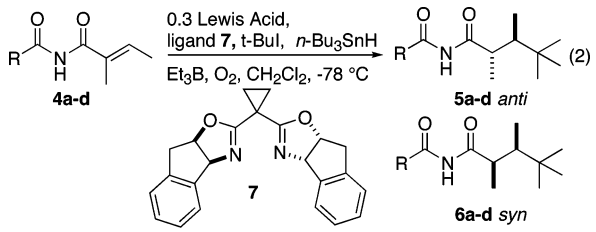
Enantioselective Lewis acid-mediated free radical reactions continue to attract interest.[1] We have recently shown that intermolecular free radical addition to β-substituted α,β-unsaturated carbonyl compounds followed by trapping with allyl stannanes can lead to two new stereocenters with high diastereo- and enantioselectivity.[2] There are few addition reactions to α,β-disubstituted enoyl systems **1** that proceed in good yield and are able to control the absolute and relative stereochemistry of both new stereocenters. This is a consequence of problematic $A^{1,3}$ interactions in either rotamer when traditional templates such as oxazolidinone are used; to relieve $A^{1,3}$ strain, the C−C bond of the enoyl group twists, breaking conjugation, which results in diminished reactivity and selectivity.[3,4] We recently reported that N−H imides[5] are excellent templates that relieve such $A^{1,3}$ problems in substrates **1**, improve reactivity for α,β-disubstituted substrates **1**, and under Lewis-acid catalysis react via the s-cis rotamer.[6] In this manuscript we demonstrate for the first time that intermolecular radical addition to α,β-disubstituted substrates followed by hydrogen atom transfer proceeds with high diastereo- and enantioselectivity (**1** → **2** or **3**, eq 1). The method is applied to the enantioselective and highly diastereoselective (99:1 dr) synthesis of *anti*-aldol-type adducts.



We began our experiments with the addition of *tert*-butyl radical to imides **4** under standard radical reductive alkylation conditions (Table 1). Racemic addition to isopropyl imide **4a** using magnesium triflimide in the absence of a chiral ligand proceeded via anti addition to give the anti product[7] **5a** in good yield and excellent diastereoselectivity (entry 1). A chiral reaction using **7** as a ligand gave the anti product with moderate enantioselectivity (entry 2). Screening of the R group on the N−H imide (entries 2−5) showed the *tert*-butyl imide template (**4d**) to give the highest enantioselectivity (entry 5) with $Mg(NTf_2)_2$-**7** as a Lewis acid. Further evaluation of several magnesium Lewis acids (entries 5−7) showed MgI_2-**7** to be optimal, giving product **5d** in good yield with excellent enantioselectivity and diastereoselectivity (entry 7). *These results clearly demonstrate that addition/trapping experiments using α,β-disubstituted enoyls as substrates can proceed with a high degree of both diastereo- and enantiocontrol.* Furthermore, they also underscore the ease with which one can vary the template leading to improved selectivity. Under the same reaction conditions, the chemical yield was <10% using oxazolidinone rather than an N−H imide as a template.

We next investigated the addition of various radicals R_1 to substrate **4d** under the optimized conditions (Table 2). Addition of a primary ethyl radical gave a moderate yield and reduced diastereoselectivity, but the enantioselectivity for the major anti product was excellent (entry 1). In contrast, reaction with the small and highly reactive methoxymethyl radical was not chemically efficient and the diastereo- and enantioselectivity were not high (entry 2). Addition/trapping with the secondary isopropyl radical gave excellent yield of the anti product in high enantioselectivity (entry 3). Similar results were also obtained using cyclohexyl radical

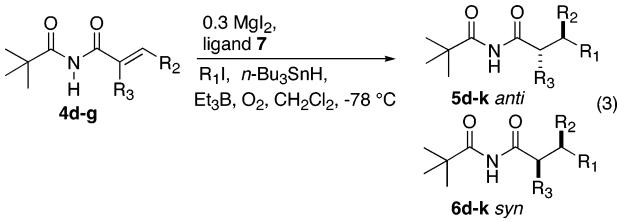
Table 1. Evaluation of Imides in Addition/Trapping Experiments[a]



entry	R	Lewis acid	ligand	yield (%)[b]	dr[c] anti/syn	ee (%)[d]
1	*i*-Pr **4a**	$Mg(NTf_2)_2$		74	98:2	
2	*i*-Pr **4a**	$Mg(NTf_2)_2$	**7**	69	97:3	69
3	cyc-hexyl **4b**	$Mg(NTf_2)_2$	**7**	67	98:2	65
4	Ph **4c**	$Mg(NTf_2)_2$	**7**	78	98:2	74
5	*t*-Bu **4d**	$Mg(NTf_2)_2$	**7**	58	96:4	83
6	*t*-Bu **4d**	$Mg(ClO_4)_2$	**7**	72	97:3	92
7	*t*-Bu **4d**	MgI_2	**7**	83	99:1	94

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Diastereomeric ratio determined by ^1H NMR (500 MHz). [d] Determined by chiral HPLC.

Table 2. Radical Additions to α,β-Disubstituted Imide Substrates



entry	R_1	R_2	R_3	SM	yield (%)[a]	product	dr **5**/**6**[b]	ee anti (%)[c]
1	Et	Me	Me	**4d**	63	**5e**/**6e**	87:13	92
2	$MeOCH_2$	Me	Me	**4d**	59	**5f**/**6f**	3:1	56
3	*i*-Pr	Me	Me	**4d**	79	**5g**/**6g**	99:1	92
4	c-Hex	Me	Me	**4d**	62	**5h**/**6h**	98:2	79
5	*t*-But	Me	Me	**4d**	83	**5d**/**6d**	99:1	94
6	*i*-Pr	Et	Me	**4e**	37	**5i**/**6i**	95:5	80
7	*i*-Pr	Ph	Me	**4f**	71	**5j**/**6j**	99:1	93
8	*i*-Pr	Me	Et	**4g**	50	**5k**/**6k**	87:13	74

[a] Isolated yield. [b] Diastereomeric ratio determined by ^1H NMR (500 MHz). [c] Determined by chiral HPLC.

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Table 3. Preparation of *anti*-Propionate Aldol-like Products

entry	mol % CLA	R_1	product	yield (%)[a]	dr[b]	ee (%)[c]
1		*i*-propyl		<5		
2	30	*i*-propyl	**9a**	79	99:1	82
3	30	*tert*-butyl	**9b**	60	99:1	90
4	30	c-hexyl	**9c**	64	99:1	70

[a] Isolated yield. [b] Diastereomeric ratio determined by ^{1}H NMR (500 MHz). [c] Determined by chiral HPLC.

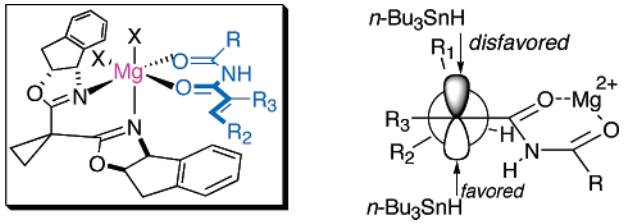

Figure 1. Model to explain enantioselectivity and diastereoselectivity.

(entry 4). As illustrated earlier, *tert*-butyl radical gave the anti isomer with outstanding selectivity (entry 5).

The impact of changing the α- and *β*-substituents on the substrate is shown in entries 6−8. A decrease in yield and diastereo- and enantioselectivity was observed on changing the *β*-substituent R_2 from a methyl group to an ethyl group (compare entry 3 with 6). However, changing the *β*-substituent to a phenyl group gave the addition/trapping product with very high selectivity (entry 7). A larger α-ethyl substituent was less well tolerated, leading to reduced selectivity (entry 8).

While many ionic routes are available for the synthesis of aldol products,[8] the neutral conditions associated with radical reactions have some appeal in terms of functional group compatibility. In addition, despite the array of solutions for the synthesis of *syn*-aldols, the number of highly selective methods for preparing *anti*-aldols is limited.[9] We have recently shown that acetate aldols are accessible through enantioselective conjugate radical additions to *β*-acyloxyenoyl oxazolidinones.[10] Initial attempts to add radicals to α-methyl-*β*-acyloxy oxazolidinones, however, gave negligible reactivity (<10%). However, greatly improved reactivity results were achieved when an N−H imide template lacking $A^{1,3}$ strain was used, making possible a highly diastereo- and enantioselective method for the preparation of *anti*-propionate aldol-like products (Table 3). These reactions have not been optimized, and the benzimide **8** rather than a *tert*-butyl imide was used because of its ease of preparation and product analysis. $Mg(ClO_4)_2$-**7** was used as the chiral Lewis acid rather than MgI_2-**7**. With all three radicals screened, yields are good, enantioselectivity is high, and the anti diastereoselectivity is outstanding (entries 2−4).

The absolute and relative stereochemistry[11] in these reactions are analogous to those observed for tandem alkylation−allylation addition to oxazolidinone cinnamate using MgI_2-**7**[2] and consistent with a model[6,2] in which initial addition to the *β*-carbon occurs from the top face opposite the aryl group of the ligand (see Figure 1). Subsequent hydrogen transfer to the α-carbon is apparently controlled not by the chiral ligand (which might be expected to block the bottom face resulting in syn addition) but by the newly formed *β*-stereocenter, with the radical R_1 group shielding the top face.[2] The diastereoselectivity is insensitive to the nature of the *β*-substituent R_2: addition of isopropyl radical occurs with 99:1 dr whether R_2 is methyl, phenyl, or benzoyloxy.[2] The insensitivity to the size or electronic character of R_2 suggests that rotameric equilibrium is minimal prior to hydrogen addition.[12,2] The diastereoselectivity does correlate the size of the radical R_1 group (Table 2).[2] Work is underway to expand the scope of this addition/trapping methodology.

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Supporting Information Available: Characterization data for compounds **4**−**9** and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Absolute and relative configurations of **5e** and **9a** were established by conversion to (**5e**) and synthesis from (**9a**) known compounds. The relative configuration of **5d** was established by conversion to a known compound. See Supporting Information for details.
(12) The observed 99:1 diastereoselectivity when R_1 = isopropyl and R_2 = phenyl (Table 2, entry 7) seems unlikely on the basis of size, given complete rotameric equilibration prior to hydrogen transfer. This model is consistent with the related observations and proposed model for alkylation−allylation additions; see ref 2. That rotameric equilibration might erode diastereoselectivity is consistent with the somewhat lower diastereoselectivities observed in ref 2 using the less reactive allyltributyltin as a radical trap.

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