

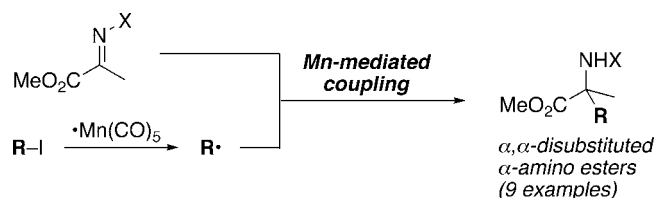
Mn-Mediated Coupling of Alkyl Iodides and Ketimines: A Radical Addition Route to α,α -Disubstituted α -Aminoesters

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ABSTRACT



Coupling of primary and secondary alkyl iodides with *N*-acylhydrazonoesters via Mn-mediated photolysis conditions affords access to *tert*-alkyl amines.

As a simple and valuable strategy for synthesis of chiral amines, the carbon–carbon bond disconnection approach involving additions to imino compounds (Figure 1) has generated some notable recent accomplishments.¹

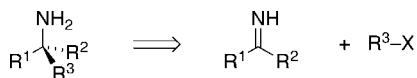


Figure 1. Carbon–carbon bond disconnection of chiral amines.

However, a significant obstacle to these additions, when strongly basic nucleophiles are used (e.g., Grignard reagents), is a competitive aza-enolization to form metalloenamines. Furthermore, the presence of other electrophilic functionality within such organometallic nucleophiles is often quite limited.

We have addressed this problem by developing Mn-mediated coupling of alkyl iodides with *N*-acylhydrazones,² exploiting conditions of notable versatility with respect to

both coupling components.³ Until now, these Mn-mediated coupling reactions have been limited to aldehyde-derived imino acceptors. However, additions to ketone-derived imino compounds⁴ are of particular interest as they could provide a diverse range of *tert*-alkyl amines not conveniently prepared by nucleophilic substitution. Here we describe the first examples of Mn-mediated coupling of diverse alkyl iodides with ketone-derived hydrazones in a route to α,α -disubstituted α -amino esters (Figure 2).

Intermolecular radical additions to aldehyde-derived imino acceptors are attracting increased attention, and a variety of

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(2) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923. Friestad, G. K.; Qin, J.; Suh, Y.; Marié, J.-C. *J. Org. Chem.* **2006**, *71*, 7016–7027.

(3) For applications in total synthesis, see: Friestad, G. K.; Deveau, A. M.; Marie, J.-C. *Org. Lett.* **2004**, *6*, 3249–3252. Korapala, C. S.; Qin, J.; Friestad, G. K. *Org. Lett.* **2007**, *9*, 4243–4246.

(4) (a) Review: Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183. (b) For examples, see: Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268–269. Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704–8708. Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Org. Chem.* **2002**, *67*, 5359–5364. Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687. Ding, H.; Friestad, G. K. *Synthesis* **2004**, 2216–2221. Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551–5553. Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743–2745. Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691. Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712–8713.

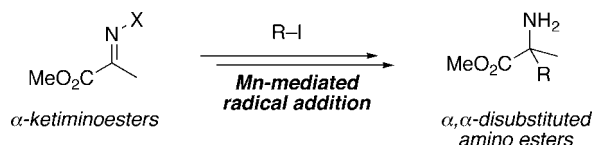
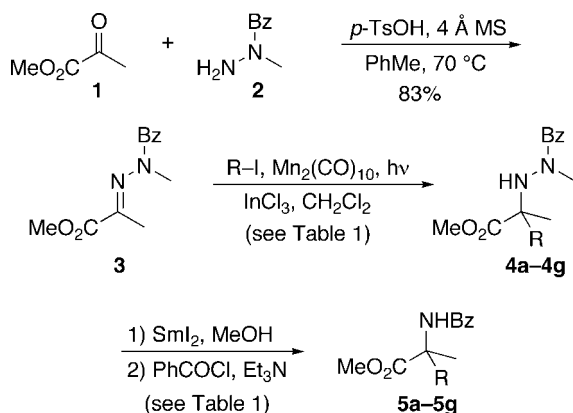


Figure 2. Mn-mediated C–C bond construction approach to α,α -disubstituted α -amino esters.

conditions may be used to achieve the additions.⁵ However, the corresponding additions to ketimine acceptors have not yet reached their synthetic potential.^{6,7} In an important seminal paper, several relevant examples were reported involving addition of alkyl iodides (15–30 equiv) to ketimine acceptors in the presence of triethylborane (5.0–7.5 equiv).⁷ Addition of simple commercial iodides (isopropyl, cyclohexyl, and *tert*-butyl) was accompanied by ethyl addition, N,C-dialkylation, and disproportionation side reactions. We hoped the versatility of our Mn-mediated coupling method (including primary and difunctional iodides more amenable to synthetic applications), reduce the amount of iodide required, and avoid all of the side reactions noted in the earlier work.⁷

Scheme 1



For initial examination of the radical additions to ketone hydrazones, a simple α -ketoester-derived *N*-acylhydrazone

(5) (a) Reviews of radical addition to C=N bonds: Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461–5496. Bertrand, M.; Feray, L.; Gastaldi, S. *C. R. Chimie* **2002**, *5*, 623–638. Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140–1157. (b) For selected recent examples, see: Cho, D. H.; Jang, D. O. *Chem. Commun.* **2006**, 5045–5047. Clerici, A.; Cannella, R.; Pastori, N.; Panzeri, W.; Porta, O. *Tetrahedron* **2006**, *62*, 5986–5994. Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87–89. Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190–6193. Risberg, E.; Fischer, A.; Somfai, P. *Tetrahedron* **2005**, *61*, 8443–8450. Friestad, G. K.; Draghici, C.; Soukri, M.; Qin, J. J. *Org. Chem.* **2005**, *70*, 6330–6338. McNabb, S. B.; Ueda, M.; Naito, T. *Org. Lett.* **2004**, *6*, 1911–1914. Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061–5063. Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461–2464.

(6) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985–1987.

was prepared. Condensation of *N*-benzoyl-*N*-methylhydrazine with methyl pyruvate afforded (*E*)-hydrazone **3** in 83% yield, with only trace amounts of the (*Z*)-hydrazone detected by ¹H NMR (*E/Z* > 99:1). With this radical acceptor in hand, Mn-mediated additions of various iodides to **3** were inspected (Table 1). Combining **3** with InCl₃ (2.2 equiv) in CH₂Cl₂,

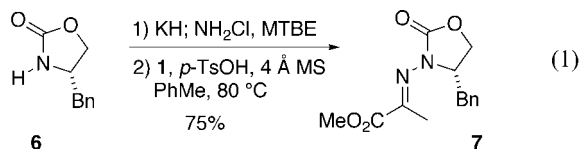
Table 1. Mn-Mediated Addition of Alkyl Iodides to *N*-Acylhydrazone **3** and N–N Bond Cleavage (Scheme 1)^a

entry	R	yield of 4 (%)	yield of 5 (%)
1	Et	44	5a , 85
2	<i>i</i> -Pr	69	5b , 98
3	<i>n</i> -C ₅ H ₁₁	63	5c , 79
4	<i>n</i> -C ₁₂ H ₂₅	57	5d , 80
5	<i>i</i> -Bu	38 ^b (51 ^c)	5e , 76
6	TBSO(CH ₂) ₂	49	5f , 95
7	TBSO(CH ₂) ₄	50 ^d (73 ^c)	5g , 94

^a Conditions: see text. ^b Recovered **3**: 25%. ^c Yield in parentheses is corrected for recovered **3**. ^d Recovered **3**: 32%.

introduction of Mn₂(CO)₁₀ (1.1 equiv) and the appropriate iodide (5 equiv), and irradiation (300 nm, Rayonet) led to the alkyl adducts **4a–4g**. The N–H bond is likely formed by H-atom abstraction from solvent.² Subsequent treatment with Sml₂/MeOH in THF smoothly cleaved the N–N bonds of these adducts to provide the corresponding free amines.⁸ These were isolated as their *N*-benzoyl derivatives in 76–98% yield.

Asymmetric induction of this process was next examined. For this purpose we chose the chiral *N*-acylhydrazone motif derived from *N*-amino-2-oxazolidinones, successfully employed previously in a variety of reactions,⁹ including stereocontrolled Mn-mediated radical additions to aldimine-type acceptors.^{2,3} Amination of the potassium salt of commercially available (*S*)-4-benzyl-2-oxazolidinone (**6**) with a solution of monochloramine in methyl *tert*-butyl ether¹⁰ (eq 1) gave a quantitative yield of the *N*-amino-2-oxazolidinone, which in turn was condensed with methyl pyruvate (**1**) to give hydrazone **7** (*E/Z* 92:8). After removal of the minor (*Z*)-isomer via flash chromatography, the (*E*)-*N*-acylhydrazone **7** was obtained in 75% yield.



Addition of ethyl iodide to (*E*)-**7** using the Mn-mediated photolysis conditions as described above gave 66% yield of

(7) (a) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324–3327. (b) Reactions reported in ref. 7a required oxygen atmosphere to minimize competing ethyl addition, and the authors noted significant hazards associated with that procedure.

(8) (a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266–6267. (b) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637–640.

(9) Review: Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157–3172.

Table 2. Effects of Lewis Acids on Mn-Mediated Addition^a

entry	R	Lewis acid	yield of 8 (%) ^b	dr of 8
1	Et	InCl ₃	66	70:30
2		In(OTf) ₃	25	51:49
3		ZnCl ₂	<3	n.d. ^c
4		Zn(OTf) ₂	53	63:37
5		La(OTf) ₃	21 (58)	42:58
6		Yb(OTf) ₃	25 (36)	34:66
7		Mg(ClO ₄) ₂	33 (57)	56:44
8		none	44 (49)	55:45
9	<i>i</i> -Pr	InCl ₃ (2.2) ^d	85	92:8
10		InCl ₃ (1.2) ^d	70	82:18
11		InCl ₃ (0.5) ^d	54	80:20
12		InCl ₃ (0.2) ^d	50	74:26

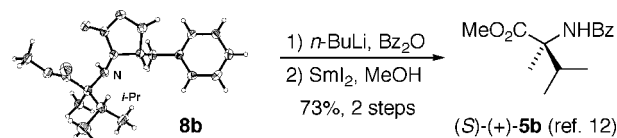
^a Conditions: see text. ^b Yield in parentheses is corrected for recovered **7**. ^c Not determined. ^d The amount of InCl₃ (equiv) is shown in parentheses.

the ethyl adduct, with diastereomer ratio of 70:30 (Table 2, entry 1). Screening a variety of Lewis acids (entries 1–7) showed that InCl₃, Zn(OTf)₂, La(OTf)₃, and Mg(ClO₄)₂ all led to similar yields of adduct **8a** (after correcting for recovered **7**), but interestingly, La(OTf)₃ and Yb(OTf)₃ inverted the diastereoselection.

With stereocontrol at modest levels and subject to inversion with different Lewis acids, these observations were sharply in contrast to prior work involving additions to aldimines.^{2,3} Thus it was of interest to gain further insight into the role of the Lewis acid. Without Lewis acid, **8a** exhibited low selectivity in ethyl addition (entry 8). Isopropyl addition occurred with much higher selectivity (entry 9); in this case the indicated configuration of adduct **8b** was determined by crystallography (**8a** was assigned by analogy).¹¹ The use of *tert*-butyl bromide was previously ineffective in Mn-mediated addition² and was not attempted here. The stoichiometry of the Lewis acid was varied (Table 2, entries 9–12), illustrating the importance of at least 2 equiv of Lewis acid for effective stereocontrol. This evidence suggests the possibility of competitive binding of Lewis acids

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(11) The configuration of the major diastereomer is consistent with radical addition to the (*E*)-hydrazone according to the proposed chelate model.² Preliminary tests show that the pure (*Z*)-hydrazone leads to the same diastereomer, suggesting in situ isomerization of the C=N bond. This point is still under investigation.

Scheme 2

to the ester functionality of **7** in addition to the two-point binding of the *N*-acylhydrazone. In light of this, Lewis acids of higher coordination number might be expected to offer anomalous results; thus the inversion of stereocontrol with lanthanide Lewis acids (entries 5 and 6) is not surprising.

Lastly, the N–N bond cleavage was achieved upon sequential treatment of isopropyl adduct **8b** with *n*-butyllithium, benzoic anhydride, and SmI₂/MeOH (Scheme 2). This sequence afforded known benzamide (*S*)-(+)-**5b**¹² in good yield, confirming the assigned configuration. Although this N–N bond cleavage employed the benzoyl group for purposes of chemical correlation of **5b**, the more synthetically useful trifluoroacetyl group can also be effective for N–N bond activation.^{8b}

The couplings of iodides and *N*-acylhydrazones described herein document the first applications of this Mn-mediated addition methodology to generation of quaternary carbon stereocenters by addition to ketimine acceptors and offer access to a variety of α -alkylated alanine analogs. With the feasibility of these Mn-mediated additions to ketimines now demonstrated, further studies are warranted. Notably, the numerous side reactions and large excesses of reagents found in the earlier work⁷ can be avoided by use of the Mn-mediated couplings presented here.

These radical additions complement enolate alkylation methodologies, as they occur under nonbasic conditions and permit introduction of both primary and secondary alkyl groups with relative ease. The versatility with respect to the iodide is a distinguishing feature of the Mn-mediated coupling that foreshadows application to more complex targets.

Acknowledgment. We thank NSF for continued support of our radical addition methodology program (CHE-0096803 and CHE-0749850).

Supporting Information Available: Preparative procedures and characterization data for compounds **3–5**, **7**, and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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