ORGANIC LETTERS

2009
Vol. 11, No. 3
765−768

Design, Synthesis, and Application of Enantioselective Coupling Reagent with a Traceless Chiral Auxiliary

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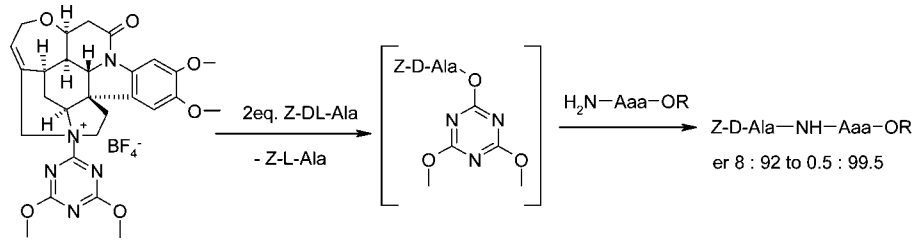
Received December 8, 2008

ABSTRACT



Stable chiral *N*-triazinylbrucinium tetrafluoroborate enantioselectively activates racemic carboxylic acids yielding enantiomerically enriched amides, esters, and dipeptides with er from 8:92 to 0.5:99.5. Due to the departure of a chiral auxiliary after the activation of the carboxylic function, all of the subsequent stages of the coupling reaction proceed without any perturbation caused by a chirality discriminator (traceless). Therefore, the advantageous coupling conditions, configuration, and enantiomeric purity of the final product are entirely predictable from the model experiment.

The rapid development of the methods of combinatorial chemistry in the systematic exploration of molecular diversity and in the search for improved activities and properties of a broad range of synthetic materials have resulted in a vigorously growing demand for numerous new chiral substrates with diversified structural features.

In most cases, enantiomerically active substrates are needed only in tiny amounts. Therefore, an approach based on the enantiodifferentiating transformation of usually easily available racemic substrates would be valued as advantageous and less time-consuming than the classic procedure involving racemate resolution or asymmetric synthesis. Such an approach would be considered the most convenient in the case of coupling chiral building blocks like amino acids used for the construction of more complex molecules.

Several chiral coupling reagents were proposed for the synthesis of enantiomerically enriched peptides directly from racemic substrates. Optically active *N*-hydroxysuccinimide[1] and diacylamine[2] derivatives were evaluated by several research groups as some of the first efficient enantioselective reagents for condensation involving racemic amino as well as carboxylic components, but none found acceptance. More promising results were obtained in kinetic resolution of racemic acylated components, mostly amines and alcohols. In several cases, high er's were obtained using the chiral component in catalytic amounts. The most spectacular results

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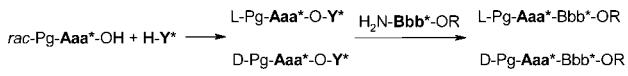
10.1021/ol802691x CCC: $40.75
Published on Web 01/07/2009

were obtained using chiral DMAP analogues,[3,4] *N*-methylimidazole,[5] benzotetramisol,[6] tertiary amines,[7] phosphines,[8] and others[9] used as a chiral auxiliary. Thus far, however, none of the proposed enantioselective coupling method was accepted for the condensations of complex molecules with stereogenic centers in both reacting components because of the unpredictable yield, purity, and configuration of the final product.

Therefore, in the presence of three chiral centers (two in both condensed substrates and one in chiral reagent or catalyst, see Scheme 1), for each pair of coupled substrates

Scheme 1



it is inevitable to select the suitable auxiliary and optimize the reaction conditions acceptable for the given synthetic goal. This limitation, which is both risky and tedious, makes this method unacceptable for the coupling of complex, expensive molecules such as peptides.

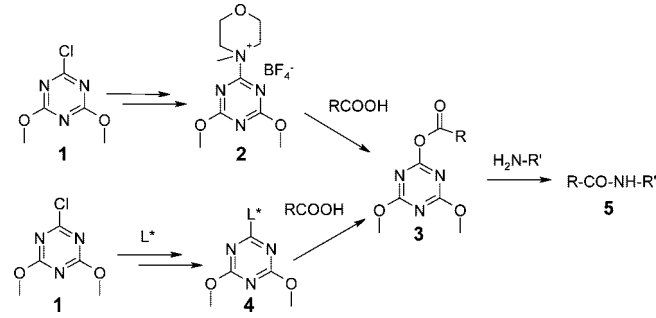
In order to overcome all the difficulties in coupling a racemic carboxylic component with a chiral nucleophile, the method of synthesis should be predictable and controllable with respect to efficiency, configuration, and enantiomeric enrichment and be applicable to the broadest possible range of substrates. Moreover, all the mentioned requirements should meet the high standards of the classic methodology of synthesis, in particular, the criterion of high enantiomeric homogeneity.[10]

In this paper, we propose an entirely new approach to enantioselective incorporation of the substrate into the chiral molecule involving a novel design of the coupling reagent. In order to remove the unpredictability of coupling results involving three chiral components, enantioselective reagents with traceless chiral auxiliary were proposed, designed, and used in experiments of kinetic resolution of racemic carboxylic component (see Scheme 2).

According to the concept, the traceless enantioselective coupling reagent **4** is a binary system consisting of a chiral auxiliary (L*) active during the enantiodiscriminating activation of the carboxylic component and subsequently departing after the completion of the process.

Thus, the structure, reactivity, and properties of the activated carboxylic component **3** should be exactly the same

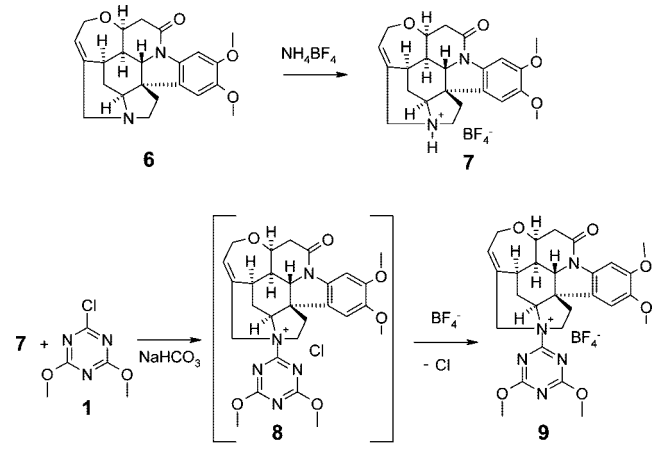
Scheme 2



as those obtained in a reaction involving a well-known, classic achiral reagent **2** with well-recognized scope and synthetic limitations (see Scheme 2). Moreover, due to the departure of the chiral auxiliary after activation, all further stages of the coupling procedure should remain free of the disturbances caused by the presence of the third chiral center, and therefore the configuration and enantiomeric purity, once established during the activation, should remain essentially intact in all the syntheses involving this carboxylic component and reagent. Thus, for the every one racemic carboxylic component all the final results of the syntheses could be predicted from the single model experiment.

The enantioselective condensing reagent was prepared in a phase transfer reaction by the treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (**1**) with brucine tetrafluoroborate (**7**) in the presence of sodium bicarbonate.[12] The postulated primary reaction product, unstable and unisolated chiral quaternary *N*-triazinylbrucinium chloride **8** bearing a chiral nitrogen atom, exchanged counterions and produced appropriate stable chiral tetrafluoroborate **9** in high yield (see Scheme 3).

Scheme 3



It has been proven in model experiments involving 2,2-dimethylpropionic acid and 4-methoxybenzoic acid that reaction with **9** gave the expected[11] "superactive esters"

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Table 1. Configuration and Enantiomeric Enrichment of Protected Peptides Obtained from Racemic Carboxylic Components with **9** Used as a Coupling Reagent

entry	racemic component	acylated component	product prepared	yield (%)	er D/L[a]
1	Z-DL-Phe	HCl·L-Ala-OMe	Z-L-Phe-L-Ala-OMe	95	3/97
2		HCl·L-Leu-OMe	Z-L-Phe-L-Leu-OMe	94.5	1/99
3		HCl·L-Trp-OMe	Z-L-Phe-L-Trp-OMe	91	0.5/99.5
4		HCl·L-Val-OMe	Z-L-Phe-L-Val-OMe	98	0.5/99.5
5		HCl·L-Ile-OBu^t	Z-L-Phe-L-Ile-OBu^t	98	0.5/99.5
6		HCl·L-Ser-OMe	Z-L-Phe-L-Ser-OMe	98	0.5/99.5
7		HCl·L-Tyr-OEt	Z-L-Phe-L-Tyr-OEt	97	05/99.5
8		2HCl·L-His-OMe	Z-L-Phe-L-His-OMe	94	0.5/99.5
9		HCl·L-Pro-OMe	Z-L-Phe-L-Pro-OMe	98	2/98
10		HCl·Gly-OEt	Z-L-Phe-Gly-OEt	85	0.5/99.5
11		NH_2-$(CH_2)_3CH_3$	Z-L-Phe-NH-$(CH_2)_3CH_3$	87	0.5/99.5
12		$NH_2-CH_2C_6H_5$	Z-L-Phe-NH-CH_2-C_6H_5	88	0.5/99.5
13		CH_3OH	Z-L-Phe-OMe	98	2/98
14	Fmoc-DL-Phe	HCl·L-Ala-OMe	Fmoc-L-Phe-L-Ala-OMe	97	05/99.5
15		HCl·L-Leu-OMe	Fmoc-L-Phe-L-Leu-OMe	98	0.5/99.5
16		HCl·Gly-OEt	Fmoc-L-Phe-Gly-OEt	90	0.5/99.5
17		NH_2-$(CH_2)_3CH_3$	Fmoc-L-Phe-NH-$(CH_2)_3CH_3$	89	0.5/99.5
18	Z-DL-Tyr	HCl·L-Leu-OMe	Z-L-Tyr-L-Leu-OMe	99	1/99
19		HCl·L-Val-OMe	Z-L-Tyr-L-Val-OMe	98	0.5/99.5
20		HCl·L-Ile-OBu^t	Z-L-Tyr-L-Ile-OBu^t	98	2/98
21		HCl·L-Ala-OMe	Z-L-Tyr-L-Ala-OMe	99	3/97
22		HCl·L-Trp-OMe	Z-L-Tyr-L-Trp-OMe	97	0.5/99.5
23		HCl·L-Phe-OMe	Z-L-Tyr-L-Phe-OMe	96	0.5/99.5
24		HCl·Gly-OMe	Z-L-Tyr-Gly-OMe	97	1.5/98.5
25		CH_3OH	Z-L-Tyr-OMe	98	2/98
26	Z-DL-Ala	HCl·L-Phe-OMe	Z-D-Ala-L-Phe-OMe	94	96/4
27		HCl·L-Leu-OMe	Z-D-Ala-L-Leu-OMe	93	93/7
28		HCl·L-Trp-OMe	Z-D-Ala-L-Trp-OMe	88	96/4
29		HCl·L-Val-OMe	Z-D-Ala-L-Val-OMe	96	98/2
30		HCl·L-Ile-OBu^t	Z-D-Ala-L-Ile-OBu^t	95	92/8
31		HCl·L-Ser-OMe	Z-D-Ala-L-Ser-OMe	93	95/5
32		HCl·L-Tyr-OEt	Z-D-Ala-L-Tyr-OEt	89	99.6/0.4
33		2HCl·L-His-OMe	Z-D-Ala-L-His-OMe	88	92/8
34		HCl·L-Pro-OMe	Z-D-Ala-L-Pro-OMe	92	97/3
35		HCl·Gly-OEt	Z-D-Ala-Gly-OEt	85	98/2
36		HCl·Aib-OMe	Z-D-Ala-Aib-OMe	88	94/6
37		NH_2-$(CH_2)_3CH_3$	Z-D-Ala-NH-$(CH_2)_3CH_3$	86	99/1
38		CH_3OH	Z-D-Ala-OMe	96	97/3
39	Fmoc-DL-Ala	HCl·L-Phe-OMe	Fmoc-D-Ala-L-Phe-OMe	92	96/4
40		HCl·L-Leu-OMe	Fmoc-D-Ala-L-Leu-OMe	93	92/8
41		HCl·Gly-OEt	Fmoc-D-Ala-Gly-OEt	87	96/4
42		NH_2-$(CH_2)_3CH_3$	Fmoc-D-Ala-NH$(CH_2)_3CH_3$	86	95/5
43	Z-DL-Val	HCl·Gly-OMe	Z-D-Val-Gly-OMe	93	99.5/0.5
44		NH_2-$(CH_2)_3CH_3$	Z-D-Val-NH-$(CH_2)_3CH_3$	90	99/1
45	Z-DL-Leu	HCl·Gly-OMe	Z-D-Leu-Gly-OMe	91	99/1
46		NH_2-$(CH_2)_3CH_3$	Z-D-Leu-NH-$(CH_2)_3CH_3$	89	99/1
47	Z-DL-nor-Leu	HCl·Gly-OMe	Z-D-nor-Leu-Gly-OMe	92	95/5
48		NH_2-$(CH_2)_3CH_3$	Z-D-nor-Leu-NH-$(CH_2)_3CH_3$	88	94/6
49	DL-Z-NH-CH$((CH_2)_4CH_3)$COOH	HCl·Gly-OMe	D-Z-NH-CH$((CH_2)_4CH_3)$CO-Gly-OMe	93	90/10
50		NH_2-$(CH_2)_3CH_3$	D-Z-NH-CH$((CH_2)_4CH_3)$CONH-$(CH_2)_3CH_3$	94	91/9
51	Z-DL-Ser	HCl·Gly-OMe	Z-L-Ser-Gly-OMe	89	5/95
52		NH_2-$(CH_2)_3CH_3$	Z-L-Ser- NH-$(CH_2)_3CH_3$	90	5.5/94.5
53	*rac*-$C_2H_5CH(C_6H_5)COOH$	NH_2-C_6H_5	(*S*)-$C_2H_5CH(C_6H_5)CO$-NH-C_6H_5	90	6/94[b]

[a] er[13] determined by GC on a ChirasilVal capillary column. [b] Determined by polarimetric method; for (*S*)-2-phenylbutanoic acid anilide $[\alpha]^{25}_D = +106$ (c = 1.0, EtOH).

2-acyloxy-4,6-dimethoxy-1,3,5-triazines **3**, which were identical with the products prepared with an achiral triazine coupling reagent.[12] In all enantioselective coupling experiments, **9** was treated with 2 equiv of a racemic carboxylic component and then, after activation, in reaction with a nucleophile, gave the final product of the condensation. After

the completion of the reaction, the chiral auxiliary, nonreacted stereodiscriminated enantiomer, and triazine byproduct were removed from the reacting mixture by the typical washing procedure. It has been found that under these conditions a high yield of HPLC pure acylated products was obtained (see Table 1).

The configuration and optical purity of isolated products were established after hydrolytic degradation to amino acids and the subsequent derivatization and separation of enantiomers by GC on a Chirasil Val capillary column. The chromatographic data confirmed that the configuration of the preferred enantiomer was identical in all the cases studied and did not depend on the structure of the acylated amino component, as it was anticipated. For N-protected aromatic amino acids, i.e., phenylalanine and tyrosine (Table 1, entries 1−25) and N-protected serine (entries 51−52), in all the experiments the L configuration was preferred. Moreover, it has to be anticipated that in all other couplings involving mentioned racemic N-protected amino acids and any kind of acylated nucleophile the L enantiomer of carboxylic component should be favored during activation, yielding a final product with er in the range 0.5/99.5 to 3/97.

For N-protected alanine (entries 26−42), valine, leucine, norleucine, and 2-aminoheptanoic acid, the D configuration was preferred (entries 43−50). Considering adverse effects such as unavoidable diastereoselection during acylation of chiral nucleohiles, diversified reaction yields altering racemic substrate/stereoselector ratio, and side reactions such as participation of anhydrides, partial racemization during coupling, and workup procedure, we did not expect identical ee's to be obtained. The most divergent ee values were found in coupling of alanine with sterically hindered substrates (entries 27 (Leu), 30 (Ile), 36 (Aib), 40 (Leu)) and acylation of less nucleophilic methanol (entries 13, 25, and 38). In the latter case, the negative effects of lowered nucleophilicity were suppressed by modification of reaction conditions and using a less reactive component in large excess.

Nevertheless, enantiomeric enrichment after coupling with **9** in all cases gave very similar results within the range of er 8/92 to er 1/99%. This documented that the departure of the chiral auxiliary prior to the acylation of the nucleophile consists a crucial advantage of **9** because this transformation substantially eliminated the unpredictable diastereomeric discriminations caused by the presence of an chiral auxiliary in reacting molecules at the coupling stage and its influence on the subsequent stages of the acylation process involving the temporary creation of new stereogenic centers in the tetrahedral intermediate.

Thus, the predictable configuration, comparable enantiomeric purity, and convenient and highly resourceful preparative procedure confirm the efficiency of the presented approach in the synthesis of enantiomerically enriched peptides, amides, and esters of carboxylic acids from racemic carboxylic components.

Acknowledgment. This study was supported by the Polish State Committee for Scientific Research under Project PBZ-KBN-126/T09/15.

Supporting Information Available: Full experimental details and spectral data for all compounds described in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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